



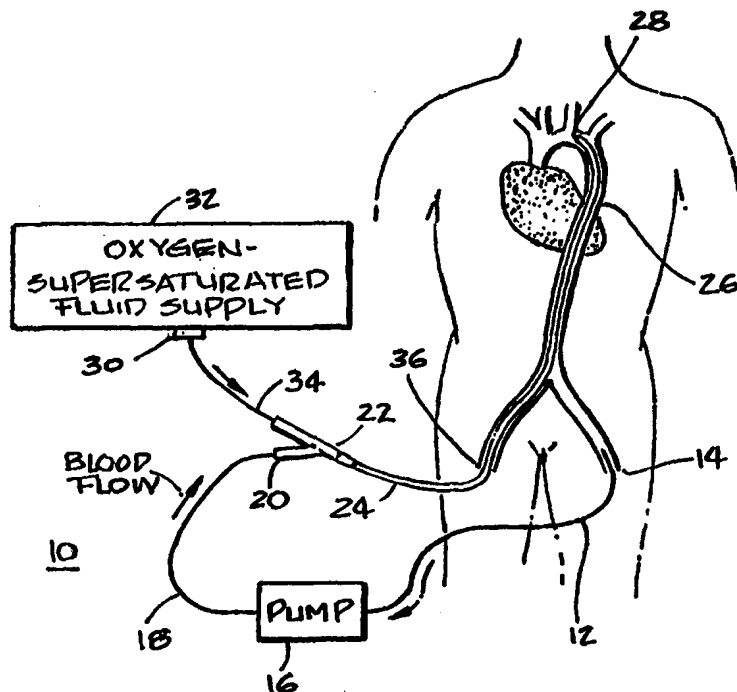
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|--|--|--|---|
| (51) International Patent Classification ⁷ : A61M 1/32, 25/00, B01F 3/04 | | A1 | (11) International Publication Number: WO 00/04943 |
| | | | (43) International Publication Date: 3 February 2000 (03.02.00) |
| (21) International Application Number: PCT/US99/16743 (22) International Filing Date: 23 July 1999 (23.07.99) (30) Priority Data: 09/122,438 24 July 1998 (24.07.98) US 09/122,143 24 July 1998 (24.07.98) US (71) Applicant: THEROX, INC. [US/US]; 2400 Michelson Drive, Irvine, CA 92612-1310 (US). (72) Inventors: DIVINO, Vincent, Jr.; 24436 Muela, Mission Viejo, CA 92692 (US). FOERSTER, Seth, A.; 758 Via Otono, San Clemente, CA 92672 (US). GESSERT, James, S.; 360 Wedgewood Court, Colorado Springs, CO 80906 (US). MEST, Robert, A.; 6102 Peabody Street, Long Beach, CA 90808 (US). ZALESKY, Paul, J.; 20292 Harpoon Circle, Huntington Beach, CA 92646 (US). SPEARS, James, R.; 615 Bridle Path Court, Bloomfield Hills, MI 48304 (US). (74) Agent: FLETCHER, Michael, G.; Fletcher, Yoder & Van Someren, P.O. Box 692289, Houston, TX 77269-2289 (US). | | (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. | |

(54) Title: METHOD AND APPARATUS FOR THE PREPARATION AND DELIVERY OF GAS-ENRICHED FLUIDS

(57) Abstract

A gas-enriched fluid is provided by the combination of a first fluid, such as a patient's blood, with a second gas-supersaturated fluid, such as an oxygen supersaturated fluid. In this example, a catheter assembly includes a portion that receives the patient's blood from a pump and that receives the oxygen supersaturated fluid from an appropriate fluid source. The oxygen supersaturated fluid is advantageously combined with the blood in an area of laminar flow, and then this gas-enriched fluid is delivered to the patient through an appropriate lumen coupled to the portion of the catheter assembly.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | | | TR | Turkey |
| BG | Bulgaria | HU | Hungary | ML | Mali | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MN | Mongolia | UA | Ukraine |
| BR | Brazil | IL | Israel | MR | Mauritania | UG | Uganda |
| BY | Belarus | IS | Iceland | MW | Malawi | US | United States of America |
| CA | Canada | IT | Italy | MX | Mexico | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NE | Niger | VN | Viet Nam |
| CG | Congo | KE | Kenya | NL | Netherlands | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NO | Norway | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | NZ | New Zealand | | |
| CM | Cameroon | | | PL | Poland | | |
| CN | China | KR | Republic of Korea | PT | Portugal | | |
| CU | Cuba | KZ | Kazakstan | RO | Romania | | |
| CZ | Czech Republic | LC | Saint Lucia | RU | Russian Federation | | |
| DE | Germany | LI | Liechtenstein | SD | Sudan | | |
| DK | Denmark | LK | Sri Lanka | SE | Sweden | | |
| EE | Estonia | LR | Liberia | SG | Singapore | | |

METHOD AND APPARATUS FOR THE PREPARATION AND DELIVERY OF GAS-ENRICHED FLUIDS

RELATED APPLICATIONS

5 This application is a continuation-in-part of U.S. patent application serial no. 08/915,532, filed on August 15, 1997, entitled "System and Method for Generalized Extracorporeal Support," by Spears *et. al*, which is incorporated herein by reference. This application is also a continuation-in-part of U.S. Patent application Serial No. 465,425, filed on June 5, 1995, entitled "Method of Delivery of Gas-Supersaturated Liquids," by Spears, which issued on August 25, 1998, as U.S.
10 Patent No. 5,797,874, which is incorporated herein by reference.

FIELD OF THE INVENTION

 The present invention relates generally to an apparatus and method for the preparation and delivery of gas-enriched fluids to gas-depleted locations, and more particularly, to a system
15 and method for the preparation and delivery of physiologic solutions for treating conditions such as tissue ischemia and post-ischemic tissues, including, *inter alia*, a catheter for delivering oxygen-enriched blood to specific locations within a patient's body.

BACKGROUND OF THE INVENTION

20 Oxygen is a crucial nutrient for human cells. Cell damage may result from oxygen deprivation for even brief periods of time, which may lead to organ dysfunction or failure. For example, heart attack and stroke victims experience blood flow obstructions or diversions that prevent oxygen from being delivered to the cells of vital tissues. Without oxygen, the heart and brain progressively deteriorate. In severe cases death results from complete organ failure. Less

severe cases typically involve costly hospitalization, specialized treatments and lengthy rehabilitation.

Blood oxygen levels may be described in terms of the partial pressure of the oxygen dissolved in the blood (pO_2). Typically, for arterial blood, normal blood oxygen levels (i.e., normoxia or normoxemia) range from 90-110 mm Hg. Hypoxemic blood (i.e., hypoxemia) is arterial blood with a pO_2 less than 90 mm Hg. Hyperoxic blood (i.e., hyperoxemia or hyperoxia) is arterial blood with a pO_2 greater than 400 mm Hg (see Cason et. al (1992), *Effects of High Arterial Oxygen Tension on Function, Blood Flow Distribution, and Metabolism in Ischemic Myocardium*, Circulation, Vol. 85, No. 2, pp. 828-838), but less than 760 mm Hg (see Shandling et al. (1997), *Hyperbaric Oxygen and Thrombolysis in Myocardial Infarction: The "HOT MI" Pilot Study*, American Heart Journal, Vol. 134, No. 3, pp. 544-550). Hyperbaric blood is arterial blood with a pO_2 greater than 760 mm Hg. Venous blood typically has a pO_2 level less than 90 mm Hg. In the average adult, for example, normal venous blood oxygen levels range generally from 40 mm Hg to 70 mm Hg.

Blood oxygen levels also might be described in terms of hemoglobin saturation levels. For normal arterial blood, hemoglobin saturation is about 97% and varies only slightly as pO_2 levels increase. For normal venous blood, hemoglobin saturation is about 75%.

In patients who suffer from acute myocardial infarction, if the myocardium is deprived of adequate levels of oxygenated blood for a prolonged period of time, irreversible damage to the heart can result. Where the infarction is manifested in a heart attack, the coronary arteries fail to provide adequate blood flow to the heart muscle.

5

Treatment of acute myocardial infarction or myocardial ischemia often comprises performing angioplasty or stenting of the vessels to compress, ablate or otherwise treat the occlusion(s) within the vessel walls. For example, a successful angioplasty increases the size of the vessel opening to allow increased blood flow.

10

Even with the successful treatment of occluded vessels, a risk of tissue injury may still exist. During percutaneous transluminal coronary angioplasty (PTCA), the balloon inflation time is limited by the patient's tolerance to ischemia caused by the temporary blockage of blood flow through a vessel during balloon inflation. Reperfusion injury also may result, for example, due to slow coronary reflow or no reflow following angioplasty.

15

For some patients angioplasty procedures are not an attractive option for the treatment of vessel blockages. Such patients typically are at increased risk of ischemia for reasons such as, poor left ventricular function, lesion type and location, or the amount of the myocardium at risk. The treatment options for such patients thus include more invasive procedures such as coronary bypass surgery.

20

To reduce the risk of tissue injury typically associated with treatments of acute myocardial infarction and myocardial ischemia, it is usually desirable to deliver oxygenated blood or oxygen-enriched fluids to at-risk tissues. Tissue injury is minimized or prevented by the diffusion of the dissolved oxygen from the blood or fluids to the tissue and/or blood perfusion that removes metabolites and that provides other chemical nutrients.

In some cases, the desired treatment of acute myocardial infarction and myocardial ischemia includes perfusion of oxygenated blood or oxygen-enriched fluids. During PTCA, for example, tolerated balloon inflation time may be increased by the concurrent introduction of oxygenated blood into the patient's coronary artery. Increased blood oxygen levels also may cause the normally perfused left ventricular cardiac tissue into hypercontractility to further increase blood flow through the treated coronary vessels.

The infusion of oxygenated blood or oxygen-enriched fluids also may be continued following the completion of PTCA treatment or other procedures (e.g. surgery) wherein cardiac tissue "stunning" with associated function compromise has occurred. In some cases continued infusion may accelerate the reversal of ischemia and facilitate recovery of myocardial function.

Conventional methods for the delivery of oxygenated blood or oxygen-enriched fluids to at-risk tissues involve the use of blood oxygenators. Such procedures generally involve withdrawing blood from a patient, circulating it through an oxygenator to increase blood oxygen concentration, and then delivering the blood back to the patient. One example of a commercially

available blood oxygenator is the Maxima blood oxygenator manufactured by Medtronic, Inc., Minneapolis, Minnesota.

There are drawbacks, however, to the use of a conventional oxygenator in an
5 extracorporeal circuit for oxygenating blood. Such systems typically are costly, complex and difficult to operate. Often a qualified perfusionist is required to prepare and monitor the system.

Conventional oxygenator systems also typically have a large priming volume, i.e., the
10 total volume of blood contained within the oxygenator, tubing and other system components, and associated devices. It is not uncommon in a typical adult patient case for the oxygenation system to hold more than one to two liters of blood. Such large priming volumes are undesirable for many reasons. For example, in some cases a blood transfusion may be necessary to compensate for the blood temporarily lost to the oxygenation system because of its large priming volume. Heaters often must be used to maintain the temperature of the blood at an acceptable level as it
15 travels through the extracorporeal circuit. Further, conventional oxygenator systems are relatively difficult to turn on and off. For instance, if the oxygenator is turned off, large stagnant pools of blood in the oxygenator might coagulate.

In addition, with extracorporeal circuits including conventional blood oxygenators there
20 is a relatively high risk of inflammatory cell reaction and blood coagulation due to the relatively slow blood flow rates and the large blood contact surface area. A blood contact surface area of about 1-2 m² and velocity flows of about 3 cm/s are not uncommon with conventional

oxygenator systems. Thus, relatively aggressive anti-coagulation therapy, such as heparinization, is usually required as an adjunct to using the oxygenator.

Perhaps one of the greatest disadvantages to using conventional blood oxygenation systems is that the maximum partial pressure of oxygen (pO_2) that can be imparted to blood with commercially available oxygenators is about 500 mm Hg. Thus, blood pO_2 levels near or above 760 mm Hg cannot be achieved with conventional oxygenators.

Some experimental studies to treat myocardial infarction have involved the use of hyperbaric oxygen therapy. See, e.g., Shandling et al. (1997), *Hyperbaric Oxygen and Thrombolysis in Myocardial Infarction: The "HOT MI" Pilot Study*, American Heart Journal, Vol. 134, No. 3, pp. 544-550. These studies generally have involved placing patients in chambers of pure oxygen pressurized at up to 2 atmospheres, resulting in systemic oxygenation of patient blood up to a pO_2 level of about 1200 mm Hg. However, use of hyperbaric oxygen therapy following restoration of coronary artery patency in the setting of an acute myocardial infarction is not practical. Monitoring critically ill patients in a hyperbaric oxygen chamber is difficult. Many patients become claustrophobic. Ear damage may occur. Further, treatment times longer than 90 minutes cannot be provided without concern for pulmonary oxygen toxicity.

For these reasons, the treatment of regional organ ischemia generally has not been developed clinically. Thus, there remains a need for a simple and convenient system for delivering oxygen-enriched blood and other fluids to patients for the localized prevention of ischemia and the treatment of post-ischemic tissue and organs.

SUMMARY OF THE INVENTION

The present invention may address one or more of the problems set forth above. Certain possible aspects of the present invention are set forth below as examples. It should be understood that these aspects are presented merely to provide the reader with a brief summary of certain forms the invention might take and that these aspects are not intended to limit the scope of the invention. Indeed, the invention may encompass a variety of aspects that may not be set forth below.

In one embodiment of the present invention, a system for the preparation and delivery of a gas-enriched fluid is provided. In applications involving the prevention of ischemia or the treatment of ischemic tissues, the system may be used for the preparation and delivery of an oxygen-enriched fluid including blood to a specific location within a patient's body. The system may include a circuit for oxygenating or enriching blood, e.g., increasing the level of dissolved oxygen in the blood. The system includes an apparatus that combines a gas-supersaturated fluid with blood to form a gas-enriched fluid, advantageously for regional or localized delivery. The gas-supersaturated fluid may include an oxygen-supersaturated physiologic liquid, and the blood to be enriched is blood withdrawn from the patient.

The system provided further includes assemblies for supplying controlled flows or supplies of the gas-supersaturated fluid and the blood. The system includes an elongated, generally tubular assembly including a central lumen and at least one end placeable within a patient body proximate a tissue site to be treated, the end including an outlet port for the gas-enriched fluid. The system may include a catheter defining a fluid pathway, including a

proximal portion adapted for coupling to supplies of gas-supersaturated fluid and blood, and a distal portion defining a fluid pathway removably insertable within a patient's body, for infusing the gas-enriched fluid to predetermined sites.

5 In an alternate embodiment of the present invention, the proximal portion of the catheter is adapted for coupling to a supply of gas-supersaturated fluid, and includes a pump loop through which blood drawn from a blood inlet flows. The blood inlet comprises a porous side segment or axial sleeve defining the entry into an annular conduit that transitions into a lumen in fluid communication with the pump loop. The inlet is disposed along the portion of the catheter
10 removably insertable within the patient's body. Upon insertion of the catheter through an access or opening, e.g., an introducer sheath, and upon its placement within the patient body, e.g., tip placement in or proximate the coronary ostium, the blood inlet is distal to the access sheath so as to permit blood from the patient to pass through and along the fluid path defined by the blood inlet, annular conduit, lumen and pump loop before combining with the gas-supersaturated fluid
15 to form the gas-enriched fluid delivered to the patient via the catheter central lumen and outlet port.

 In another embodiment of the present invention, a method is provided for the preparation and delivery of a gas-enriched fluid. In applications involving the prevention of ischemia or the
20 treatment of ischemic tissues, the method may include the step of combining a gas-supersaturated fluid with blood to form a gas-enriched fluid. Advantageously, the gas-supersaturated fluid comprises an oxygen-supersaturated physiologic liquid in which oxygen is dissolved at concentrations normalized to standard temperature and pressure (STP) that equal or exceed the

volume of the solvent. Examples of solvents which may be used include saline, lactated Ringer's, and other water-based physiologic solutions.

In accordance with another embodiment of the present invention, a method is provided for delivering an oxygen-enriched fluid to a specific site within a patient's body. The method comprises raising the pO_2 level of the fluid to be supplied to the patient. Where the fluid to be infused includes blood, the method may include the step of controlling or providing controlled amounts of the blood and oxygen-supersaturated fluid that are combined so as to produce an oxygen-enriched fluid for delivery to a specific predetermined site. Blood pO_2 levels may be maintained, adjusted, or otherwise controlled by controlling the flow rates or by providing controlled amounts of the blood and/or oxygen-supersaturated fluid. Thus, a blood-gas control method is provided.

Furthermore, delivery of the gas-enriched fluid advantageously occurs without the formation of clinically significant bubbles. To help minimize or eliminate the formation of clinically significant bubbles, the blood contact surfaces are exposed to or coated with blood proteins for some brief time interval, usually at least several minutes, before the start of infusion of oxygen-supersaturated fluid. Also, fluid contact surfaces are exposed to or pre-wetted with liquids, e.g., saline, ethanol and benzalkonium heparin, before use. The fluid contact surfaces also do not include any substance which promotes such bubble formation, e.g., hydrophobic surfaces that are difficult to wet, teflon, teflon-composite liners, silicone oils, etc. Hydrophillic fluid contact surfaces are typically useful.

The embodiments may be used in conjunction with angiographic or guiding catheters, arterial sheaths, and/or other devices used in angioplasty and in other interventional cardiovascular procedures. The system may be used in applications involving one or more vascular openings, i.e., in either contralateral or ipsilateral procedures.

5

In contralateral procedures blood is withdrawn from the patient at a first location, e.g., the left femoral artery. The blood is enriched and then is returned to the patient at a second location proximate the tissue to be treated. Blood enrichment occurs as the blood pumped through the extracorporeal circuit or loop is combined with the gas-supersaturated fluid to form the gas-enriched fluid to be delivered. In applications where the system includes a catheter, the catheter may include proximal and distal ends and a central lumen. The proximal end is adapted for the catheter to receive a supply of the gas-supersaturated fluid and to receive the blood. The distal end is removably insertable within a patient's body through a second location such as the patient's right femoral artery. The distal end includes at least one port in fluid communication with the central lumen and through which the gas-enriched fluid may exit. Further, the distal portion of the catheter may be adapted with a tip portion shaped so as to promote insertion of the device, such as through the same sheath used for interventional procedures like angioplasty, to specific predetermined locations within a patient's body. Examples of tip portion shapes which may be used include any of the standard clinically accepted tip configurations used with devices like guide catheters for providing access to and for holding in locations like the coronary ostium. Accordingly, the method may further include the step of positioning the portion of the distal end of the catheter including the fluid exit port at a predetermined location within a patient body proximate to the tissue to be treated.

10

15

20

In ipsilateral procedures, the system may be used along with one or more of any of a number of suitable, standard-size, clinically accepted guide catheters and/or introducer sheaths. The system, for example, may comprise a catheter, a catheter and guide catheter, or a catheter and sheath, for use within a guide catheter or introducer sheath used for the primary
5 interventional procedure. In accordance with this embodiment of the present invention, blood is drawn between the catheter and guide catheter or sheath assemblies of the present invention, between the catheter assembly of the present invention and the guide catheter or introducer sheath used for the primary interventional procedure, or from the annular space between the guide catheter and the introducer sheath.

10 As described herein, the preferred gas-supersaturated fluid for use in accordance with the present invention is an oxygen-supersaturated fluid. However, other fluids may be used depending upon the circumstances involved in a particular desired application, such as, for example, supersaturated fluids in which one or more gases such as helium, nitrous oxide, carbon
15 dioxide and air are dissolved. The oxygen-supersaturated fluid may include a dissolved oxygen volume normalized to standard temperature and pressure of between about 0.5 and about 3 times the volume of the solvent. The fluid is supplied to the system at a pressure of between about 250 p.s.i. and about 5000 p.s.i. The exact pressure may vary depending upon the circumstances involved in a particular application. Further, the oxygen-supersaturated fluid supplied may be a
20 sterile fluid which does not include gas, surface, or bubble nucleation sites at which clinically significant bubbles may form.

Exemplary apparatus and methods for preparing oxygen-supersaturated fluids are disclosed in U.S. Patent No. 5,407,426 to Spears entitled "Method and Apparatus for Delivering Oxygen into Blood"; U.S. Patent No. 5,569,180 to Spears entitled "Method for Delivering a Gas-Supersaturated Fluid to a Gas-Depleted Site and Use Thereof"; and U.S. Patent No. 5,599,296 to Spears entitled "Apparatus and Method of Delivery of Gas-Supersaturated Liquids"; each of which is incorporated herein by reference. Furthermore, disclosure relating to exemplary apparatus and methods for the preparation and/or use of gas-supersaturated fluids, including, e.g., oxygen-supersaturated fluids, in various applications, may be found in the following patents and patent applications, each of which is incorporated herein by reference:

copending U.S. patent application serial no. 08/465,425, filed June 5, 1995, now U.S. Patent No. 5,797,874, which is a division of U.S. patent application serial no. 353,137, filed December 9, 1994, now U.S. Patent No. 5,599,296, which is a continuation in part of U.S. patent application serial no. 273,652, filed July 12, 1994, now U.S. Patent No. 5,569,180, which is a continuation in part of U.S. patent application serial no. 152,589, filed November 15, 1993, now U.S. Patent No. 5,407,426, which is a continuation in part of U.S. patent application serial no. 818,045, filed January 8, 1992, now U.S. Patent No. 5,261,875, which is a continuation of U.S. patent application serial no. 655,078, filed February 14, 1991, now U.S. Patent No. 5,086,620;

copending U.S. patent application serial no. 08/581,019, filed January 3, 1996, which is a continuation in part of U.S. patent application serial no. 273,652, filed July 12, 1994, now U.S. Patent No. 5,569,180, which is a continuation in part of U.S. Patent application serial no. 152,589, filed November 15, 1993, now U.S. Patent No. 5,407,426, which is a continuation in

part of U.S. patent application serial no. 818,045, filed January 8, 1992, now U.S. Patent No. 5,261,875, which is a continuation of U.S. patent application serial no. 655,078, filed February 14, 1991, now U.S. Patent No. 5,086,620; and

5 copen pending U.S. patent application serial no. 08/840,908, filed April 16, 1997, which is a continuation in part of U.S. patent application 453,660, filed May 30, 1995, now U.S. Patent No. 5,735,934, which is a division of U.S. patent application serial no. 273,652, filed July 12, 1994, now U.S. Patent No. 5,569,180, which is a continuation in part of U.S. Patent application serial no. 152,589, filed November 15, 1993, now U.S. Patent No. 5,407,426, which is a continuation
10 in part of U.S. patent application serial no. 818,045, filed January 8, 1992, now U.S. Patent No. 5,261,875, which is a continuation of U.S. patent application serial no. 655,078, filed February 14, 1991, now U.S. Patent No. 5,086,620.

15 The catheter system of the present invention is typically sized in accordance with the circumstances involved in a particular application. In general, the sizes of the various system components will be on the order of the sizes of clinically accepted interventional cardiovascular devices. Usually, the extracorporeal loop of the present invention is less than four meters in total length. Thus, for example, where the system supports blood flow rates between 100 ml/min and 175 ml/min, the priming volume would be approximately 35 ml.

BRIEF DESCRIPTION OF THE DRAWINGS

Further objects and advantages of the present invention will become apparent upon reading the following detailed description and upon referring to the accompanying drawings in which:

5

FIG. 1 is a schematic diagram of an exemplary embodiment of a catheter system used in a contralateral interventional procedure in accordance with the present invention.

10

FIG. 2 is a cross-sectional view of part of an exemplary embodiment of a catheter system including an angled blood flow path in accordance with the present invention.

FIG. 3 is a cross-sectional view of part of an alternate exemplary embodiment of a catheter system including an angled blood flow path in accordance with the present invention.

15

FIG. 4 is a cross-sectional view of part of another exemplary embodiment of a catheter system including a straight blood flow path in accordance with the present invention.

20

FIG. 4A is a cross-sectional view along line A-A in FIG. 4 of the exemplary embodiment of a catheter system including a straight blood flow path shown in accordance with the present invention.

FIG. 5 is a perspective view of part of an exemplary embodiment of a catheter system including an exemplary oxygen-supersaturated fluid outlet in accordance with the present invention.

5 FIG. 5A is a cross-sectional view along line A-A in FIG. 5 of the part of the exemplary embodiment of a catheter system including an exemplary oxygen-supersaturated fluid outlet shown in accordance with the present invention.

10 FIG. 5B is a view of the exemplary oxygen-supersaturated fluid outlet shown in FIG. 5 in accordance with the present invention.

FIG. 6 is a cross-sectional view of part of an exemplary embodiment of a catheter system including an integrated blood inlet introducer sheath in accordance with the present invention.

15 FIG. 7 is a schematic diagram of an exemplary embodiment of a catheter system for use in an ipsilateral interventional procedure in accordance with the present invention.

20 FIG. 8 is a cross-sectional view of part of an exemplary guide catheter including a liner used with an exemplary embodiment of a catheter system in accordance with the present invention.

FIG. 8A is a cross-sectional view of the exemplary guide catheter shown in FIG. 8, without the liner, in accordance with the present invention.

FIG. 9 is a cross-sectional view of part of an exemplary catheter system including an integral blood draw comprising a porous side blood inlet in accordance with the present invention.

5 FIG. 10 is a cross-sectional view of part of an exemplary catheter system including an integral blood draw comprising an axial blood inlet in accordance with the present invention.

FIG. 10A is a cross-sectional view along line A-A in FIG. 10 of the part of an exemplary catheter system shown in accordance with the present invention.

10

FIG. 11 is a view of part of an alternate exemplary catheter system including an integral blood draw comprising a porous side blood inlet in accordance with the present invention.

15 FIG. 11A is a cross-sectional view along line A-A in FIG. 11 of part of an alternate exemplary catheter system including an integral blood draw comprising a porous side blood inlet in accordance with the present invention.

20 FIG. 11B is a cross-sectional view along line B-B in FIG. 11 of part of an alternate exemplary catheter system including an integral blood draw comprising a porous side blood inlet in accordance with the present invention.

FIG. 11C is a cross-sectional view along line C-C in FIG. 11 of part of an alternate exemplary catheter system including an integral blood draw comprising a porous side blood inlet in accordance with the present invention.

5 FIG. 11D is a cross-sectional view along line D-D in FIG. 11 of part of an alternate exemplary catheter system including an integral blood draw comprising a porous side blood inlet in accordance with the present invention.

10 FIG. 12 is a cross-sectional view of an exemplary tip configuration of a catheter in accordance with the present invention.

FIG. 12A is a cross-sectional view along line A-A in FIG. 12 of an exemplary tip configuration of a catheter in accordance with the present invention.

15 FIG. 12B is a cross-sectional view along line B-B in FIG. 12 of an exemplary tip configuration of a catheter in accordance with the present invention.

FIG. 13 is a cross-sectional view of an alternate exemplary tip configuration of a catheter in accordance with the present invention.

20 FIG. 13A is a cross-sectional view along line A-A in FIG. 13 of an alternate exemplary tip configuration of a catheter in accordance with the present invention.

FIG. 13B is a cross-sectional view along line B-B in FIG. 13 of an alternate exemplary tip configuration of a catheter in accordance with the present invention.

FIG. 14 is a cross-sectional view of an alternate exemplary tip configuration of a catheter
5 in accordance with the present invention.

FIG. 14A is a cross-sectional view of a further alternate exemplary tip configuration of a catheter in accordance with the present invention.

10 FIG. 15 is an isometric view of an exemplary bubble detector transducer in accordance with the present invention.

FIG. 15A is a partially exploded view of a portion of the bubble detector transducer shown in FIG. 15.

15 The present invention may be susceptible to various modifications and alternative forms. Specific embodiments of the present invention are shown by way of example in the drawings and are described herein in detail. It should be understood, however, that the description set forth herein of specific embodiments is not intended to limit the present invention to the
20 particular forms disclosed. Rather, all modifications, alternatives, and equivalents falling within the spirit and scope of the invention as defined by the appended claims are intended to be covered.

DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS

The description below illustrates embodiments of the present invention. For the sake of clarity, not all features of an actual implementation of the present invention are described in this specification. It should be appreciated that in connection with developing any actual
5 embodiment of the present invention many application-specific decisions must be made to achieve specific goals, which may vary from one application to another. Further, it should be appreciated that any such development effort might be complex and time-consuming, but would still be routine for those of ordinary skill in the art having the benefit of this disclosure.

10 For the sake of clarity and convenience, the various embodiments are described herein in the context of interventional cardiovascular applications generally involving acute or transient ischemia or post-ischemic tissues. However, the present invention may also be useful in other medical applications, such as cancer therapy (e.g., the delivery of oxygen-enriched fluids directly into poorly vascularized tumors during radiation or chemotherapy treatments), neurovascular
15 applications (e.g., the treatment of stroke and cerebral trauma patients), lung support in trauma and lung disease patients, and wound care management.

Also, although the present invention may be used to raise oxygen levels, for example, in venous and arterial blood, in blood substitutes, e.g., perfluorocarbons, and in combinations
20 thereof, for the sake of clarity and convenience reference is made herein only to arterial blood.

Further, the present invention also may be used in connection with drug fluid infusion therapies. Examples of drug fluids used in cardiovascular and neurological procedures which

may be infused in accordance with the present invention include, without limitation, vasodilators (e.g., nitroglycerin and nitroprusside), platelet-actives (e.g., ReoPro and Orbofiban), thrombolytics (e.g., t-PA, streptokinase, and urokinase), antiarrhythmics (e.g., lidocaine, procainamide), beta blockers (e.g., esmolol, inderal), calcium channel blockers (e.g., diltiazem, verapamil), magnesium, inotropic agents (e.g., epinephrine, dopamine), perfluorocarbons (e.g., fluosol), crystalloids (e.g., normal saline, lactated ringers), colloids (albumin, hespan), blood products (packed red blood cells, platelets, whole blood), Na⁺/H⁺ exchange inhibitors, free radical scavengers, diuretics (e.g., mannitol), antiseizure drugs (e.g., phenobarbital, valium), and neuroprotectants (e.g., lubeluzole).

Turning now to the drawings, a system is provided in which blood is combined with an oxygen-supersaturated fluid to form an oxygen-enriched fluid that may be delivered to a particular predetermined area within a patient's body for the treatment of conditions such as tissue ischemia and post-ischemic tissues. As shown in Fig. 1, one embodiment of such a system includes a blood draw 12 comprising a continuous fluid flow path between a vascular access site 14 of a patient body and a pump 16. The selection of the vascular access site typically is made by a physician or caregiver and depends upon the circumstances surrounding the particular application involved. The particular vascular access site illustrated in Fig. 1 is the left femoral artery. The blood pump 16 may be one of the many commercially available and clinically accepted blood pumps suitable for use with human patients. An example of one such pump is the Model 6501 RFL3.5 Pemco peristaltic pump available from Pemco Medical, Cleveland, Ohio.

The pump 16 draws blood from the patient and provides a supply of blood via line 18 to the inlet 20 of catheter 22. The flow characteristics of the blood will depend upon the circumstances surrounding the particular application involved. Typically, the supply of blood to the blood inlet 20 of catheter 22 will be a controlled flow defined by the flow parameters selected by the caregiver. Factors influencing the determination of blood flow characteristics may include one or more of the many clinical parameters or variables of the blood to be supplied to the catheter or of the oxygen-enriched fluid to be delivered to the patient, e.g., the size of the patient, the percentage of overall circulation to be provided, hemolysis, hemodilution, pO_2 , pulsatility, mass flow rate, volume flow rate, temperature, hemoglobin concentration and pH.

The system 10 may include one or more gas bubble detectors, at least one of which is capable of detecting the presence of microbubbles, i.e., bubbles with diameters of about 7 to 10 microns to about 200 microns (see, e.g., Fig. 12). In addition, the system may include one or more macrobubble detectors to detect larger bubbles, such as bubbles with diameters of 1 millimeter or more. Such macrobubble detectors may comprise any suitable commercially available detector, such as an outside, tube-mounted bubble detector including two transducers measuring attenuation of a sound pulse traveling from one side of the tube to the other. One such suitable detector may be purchased from Transonic Inc. of New York. The microbubble and macrobubble detectors provide the physician or caregiver with a warning of potentially clinically significant bubble generation. The system 10 also may include various conventional items, such as sensors, flow meters (which may also serve a dual role as a macrobubble detector), or other clinical parameter monitoring devices; hydraulic components such as accumulators and valves for managing flow dynamics; access ports which permit withdrawal of fluids; filters or other

safety devices to help ensure sterility; or other devices that generally may assist in controlling the flow of one or more of the fluids in the system 10. Advantageously, any such devices are positioned within the system and used so as to avoid causing the formation of clinically significant bubbles within the fluid flow paths.

5

The catheter 22 includes a proximal portion 24 and a distal portion 26, the distal portion being removably insertable within a patient body through a vascular access or opening 36. The proximal portion 24 includes blood inlet 20. Blood inlet 20 and line 18 may be adapted for releasably coupling, e.g., with a clinically accepted fluid connection apparatus such as a Luer lock, to enable the catheter 22 to receive the blood supplied via line 18. The catheter 22 includes a lumen defining a continuous blood flow path from the blood inlet 20 to a fluid exit port proximate the distal tip 28 of catheter 22.

10

The proximal portion 24 of catheter 22 also includes a fluid inlet port 30 adapted to couple to a supply 32 of oxygen-supersaturated fluid. The port 30 is in fluid communication with the supply 32 and with line 34. Line 34 comprises one or more capillaries or other elongated generally tubular members including central lumens, either alone or in an array, each defining a continuous fluid flow path between port 30 and the blood flow path of the catheter 22.

15

The oxygen-supersaturated fluid is usually supplied to port 30 in accordance with parameters specified and selected by the caregiver for the desired clinical indication. The flow of oxygen-supersaturated fluid is generally steady and continuous, although variable or intermittent flows may be used. Flow rates may range from about 0.1 cc/min to about 40 cc/mm, although

20

particularly advantageous flow rates may be between about 2 cc/min and 12 cc/min. Oxygen concentrations may range from about 0.5 cc O₂ per cc physiologic solution to about 3 cc O₂ per cc physiologic solution, although particularly advantageous concentrations may be about 1 cc O₂ per cc physiologic solution. The oxygen-supersaturated fluid is provided at a temperature such that when the fluid combines with blood to form the oxygen-enriched fluid to be infused, the oxygen-enriched fluid is about 37°C, i.e., system operation does not significantly affect patient blood temperature.

Figure 2 shows an embodiment in which catheter portion 40 comprises a section of the catheter in which the flows of blood and oxygen-supersaturated fluid combine. Catheter portion 40 comprises the proximal end of an elongated tubular member 48, including a generally centrally disposed fluid return lumen 52, disposed within a housing 42 including a blood inlet lumen 44. Lumen 44 defines a continuous fluid flow path between catheter blood inlet port 46 and the proximal end 50 of fluid return lumen 52. The distal portion of member 48 (not shown) is removably insertable within a patient body and includes the exit port through which fluid traveling within fluid return lumen 52 is delivered to a site within a patient's body.

Housing 42 typically comprises a biocompatible, molded polymeric material. The exact size and shape of housing 42 may vary depending upon the circumstances involved in a particular application. Figure 2, by way of example, shows a generally y-shaped configuration. The tubular member 48 may be integrally formed with housing 42. However, tubular member 48 may comprise clinically approved polymeric tubing. The proximal end of member 48 is fixedly

attached within housing 42. Typically, the joining of housing 42 and member 48 is accomplished by solvent or adhesive bonding or insert or over molding.

The size and shape of lumen 44 also may vary depending upon the circumstances involved in a particular application. Fig. 2, by way of example, shows a lumen 44 defining an angled blood flow path. However, a straight or curved blood flow path might also be used. See, e.g., Fig. 4. Advantageously, any difference between the inner diameter of the proximal end of member 48 and the diameter of lumen 44 at the proximal end 50 of fluid return lumen 52 is minimized or eliminated to promote smooth blood flow.

Catheter portion 40 also includes the distal portion of an oxygen-supersaturated fluid delivery line 54. The line 54 comprises at least one elongated generally tubular member including a central lumen defining a fluid flow path between a fluid inlet port (not shown in Fig. 2) disposed at the proximal end of line 54 and fluid exit port 56 disposed at the distal end 58 of line 54. Catheter portion 40 also may include one or more stress/strain relief assemblies 60, 62.

The proximal end of line 54 may be adapted to releasably couple to a supply of oxygen-supersaturated fluid. The fluid exit port 56 may be disposed within the flow path defined by fluid return lumen 52. Thus, a continuous fluid flow path is defined between the supply of oxygen-supersaturated fluid and a predetermined site within a patient's body proximate the distal end of fluid return lumen 52.

The portions proximate to fluid exit port 56 of fluid return lumen 52 and of the distal end 58 of line 54 are generally straight, and their longitudinal axes approximately coincide, so that any difference in the direction of blood flow in lumen 52 proximate port 56 and the direction of exit fluid flow through port 56 is minimized or eliminated.

5

As shown in Fig. 2, fluid exit port 56 may be sufficiently downstream of the proximal end 50 of fluid return lumen 52 that the fluid exiting port 56 avoids any fluid flow disruption or non-laminar flow associated with the boundary between housing 42 and member 48 that might cause the formation of clinically significant gas bubbles. However, where any such flow disruptions or non-laminar flows are minimized or eliminated, the exit port for the oxygen-supersaturated fluid may be disposed upstream of the proximal end of the fluid return lumen. See, e.g., Figs. 3 and 4. Further, as shown in Fig. 3, in an alternate embodiment, an oxygen-supersaturated fluid line 64 may include a distal portion 66 including a fluid exit port 68 at the outer boundary of lumen 44. For example, as shown in Fig. 3, the longitudinal axis of line 64 proximate port 68 and the longitudinal axis of the portion of lumen 44 downstream of port 68 advantageously coincide, while the longitudinal axis of line 64 proximate port 68 and the longitudinal axis of the portion of lumen 44 upstream of port 68 advantageously form an angle 70 comprising an acute angle which permits the smooth introduction of fluid from line 64 into the blood flow through lumen 44. Advantageously, the angle 70 may be about thirty degrees, for instance.

10

15

20

As shown in Fig. 2, the portion of line 54 extending from housing 42 into the blood flow path may be rigid enough to comprise a cantilever-like member. However, as shown in Fig. 4, the extending portion of the oxygen-supersaturated fluid flow line 76 also may comprise a more flexible member which tends to align itself naturally within blood flow lumen 74 along the path of least resistance. The distal end of line 76 may be supported in place or otherwise oriented within the lumen 74 by one or more wings 72 extending between the distal end of oxygen-supersaturated line 76 and the outer wall or boundary defining lumen 74. The flexibility and positioning of the lines 54 and 76 depend upon the circumstances involved in a particular application, e.g., the material hardness, line profile, the number of capillaries making up the line, and the desired fluid exit location.

The oxygen-supersaturated fluid is injected so as to minimize or avoid altogether blood cell damage. An exemplary oxygen-supersaturated fluid outlet is shown in Fig. 5. The oxygen-supersaturated fluid line 80 is disposed within fluid delivery lumen 84. The distal tip of line 80 is oriented within lumen 84 by one or more ribs or spacers 82 securing the distal portion of line 80. The line 80 includes one or more capillaries 86 (see Fig. 5B) each including a central lumen 88 through which oxygen-supersaturated fluid flows. The configuration of the distal tip of line 80 advantageously minimizes or eliminates flow disruptions resulting from the exit of fluid from each lumen 88 into the flow of blood within lumen 84. By way of example, Fig. 5B shows a line 80 comprising four capillaries 86 and including a distal tip of generally conical shape. The ends of each capillary 86 may form an included angle 90 of about 52 degrees, for instance. The capillaries may be made of glass sheathed in polyimide, with ground and polished distal ends to help minimize or eliminate the formation of clinically significant bubbles and fluid flow

disruptions. The line 80 may include four 100 micron inner diameter by 350 micron outer diameter tubes, for instance, potted together with epoxy at their proximal and distal ends. However, the inner diameter may be in the range of about 20 to about 1000 microns, with an inner diameter of about 100 to about 125 microns being particularly advantageous. Of course the exact size and shape of the distal end and tip of line 80 may vary depending upon the circumstances involved in a particular application. Examples of possible configurations include, without limitation, flat, blunt, squared, pencil-shaped, curved, parabolic, hyperbolic, and pyramidal.

In the embodiment shown in Fig. 6, the catheter includes an oxygen-enriched fluid return line 100 and a blood draw assembly comprising a sheath 102 and housing 104. The housing 104 includes a lumen 106 which forms a blood flow path between the lumens of sheath 102 and tube 108. Tube 108 comprises the line which supplies blood to the blood pump (not shown in Fig. 6) of the system. The line 100 is generally centrally disposed through the housing 104 and within the central lumen of the sheath 102. Upon insertion of the distal portion of line 100 into a patient's body, the sheath 102 is positioned within a vascular access sheath, guide catheter, or other such access device, so that blood from the patient may enter the annular space 110 between the outer wall of line 100 and the inner wall of sheath 102. The proximal end of line 100 may include a stress/strain relief assembly 112.

Figure 7 is a schematic diagram illustrating a use of the catheter system with a separate arterial access sheath 114. The sheath 114 may be one of the many sizes and types of clinically accepted arterial access sheaths suitable for use in interventional cardiovascular procedures. The

proximal end 116 of sheath 114 is adapted with a seal or other such device which permits the insertion of catheters, guidewires, or other interventional devices through the sheath 114 and into the body without unnecessary loss of blood. Blood drawn through the lumen 118 of sheath 114 travels via line 120 to blood pump 122 before being enriched and returned to the body. The blood returns via line 124 and the catheter portion 126, where the blood flow combines with a flow of oxygen-supersaturated fluid delivered via line 128 from a supply 130 to form the oxygen-enriched fluid delivered to the patient via the distal portion 132 of the catheter system.

Figures 8 and 8A show an alternate embodiment of the catheter system. In accordance with this embodiment, a guide catheter 140 including a distal tip (not shown) removably insertable within a patient's body is placed through an outer arterial access sheath 142. The sheath 142 may be any one of the many types of clinically accepted sheaths typically used in interventional cardiovascular procedures to gain access to a patient's vasculature. The guide catheter 140 includes a liner 144. The liner 144 is deformable and may be either partially (not shown) or completely (see Fig. 8A) removed. When a positive pressure is applied to lumen 146 of guide catheter 140, e.g., when angiographic dyes are introduced into the lumen 146, and when the liner 144 is in place covering the blood inlet holes 148 through the wall of guide catheter 140, the liner 144 presses against and closes inlet holes 148. When a negative pressure is applied to lumen 146 of guide catheter 140, e.g., during the withdrawal of blood from the patient, the liner deforms as necessary to allow the entry of blood into lumen 146 through inlet holes 148.

To facilitate the draw of blood from the patient, the fluid return line 150 may include a proximal portion 152 having smaller internal and external diameters than the distal portion 154 of line 150. When the distal tip of line 150 (not shown) is in place within the patient's body proximate a predetermined site, the transition region 156 is disposed downstream of blood inlet holes 148 so as to permit the entry of blood into lumen 146. The transition region 156 comprises a section of the line 150 in which the external and internal diameters of the line 150 increase along its length. To minimize or eliminate the formation of clinically significant bubbles, downstream of transition region 156 the flow of blood in line 150 combines with oxygen-supersaturated fluid exiting at the end 158 of oxygen-supersaturated fluid supply tube 160. As described herein (see, e.g., Fig. 5), the tube 160 may comprise either a single capillary or tube, or a bundle of capillaries or tubes.

Figure 9 describes part of a catheter system including an integral blood draw comprising an annular porous side blood inlet 170. The catheter 172 may be used along with a guide catheter or access sheath (not shown in Fig. 9). Blood is drawn from the patient and through the inlet 170 into catheter outer lumen 174. From there, the blood circulates through a blood pump and is delivered back to the patient via catheter inner lumen 176. As shown in Fig. 9, the inner lumen 176 includes a proximal portion 178 having relatively smaller internal and external diameters than distal portion 180, and a transition region 182 joining the two portions. Oxygen-supersaturated fluid supply tube 184 includes a fluid exit port 186 disposed within the distal portion 180 of catheter 172. The fluid exiting tube 184 enters the blood flow within lumen 176 downstream of any sharp pressure drops or other flow disturbances associated with the increase

in the inner diameter of lumen 176 in the transition region 182. Ribs or wings 188 or another such centering device may be used to hold the distal portion of tube 184 in place.

In an alternate embodiment, as shown in Fig. 10, the integral blood inlet of a catheter 190 comprises an axial blood inlet 192. Blood from the patient is drawn from the interior of a guide catheter or sheath, or directly from the patient's vasculature, through the inlet 192, and into catheter outer lumen 194. From there the blood travels through a blood pump (not shown) and is returned to the patient via inner lumen 196. As shown in Fig. 10, the inner lumen 196 includes a proximal portion 198 having relatively smaller internal and external diameters than distal portion 200, and a transition region 202 joining the two portions. Oxygen-supersaturated fluid supply tube 204 includes a fluid exit port 206 disposed within the distal portion 200 of catheter 190, and ribs or wings 208 may be used to hold the distal portion of tube 204 in place. The proximal portion 198 of inner lumen 196 may be fixed within the interior of outer lumen 194 by a further set or ribs or wings or other similar positioning device. As shown in Fig. 10, the proximal portion 198 of lumen 196 is free to naturally follow a path of least resistance through lumen 194. The proximal portion of tube 204 likewise may be secured within lumen 196 or be free as shown.

Figures 11 and 11A-D show part of an alternate exemplary catheter system including an integral blood draw. A porous side blood inlet 210 comprising a plurality of channels 212 through the outer wall of catheter 214 allows blood from the patient to enter outer lumen 216. The blood in lumen 216 passes through a blood pump (not shown in Fig. 11) before returning to the patient via lumen 218. Within lumen 218 the blood combines with an oxygen-supersaturated fluid supplied via a tube 220. As shown in Fig. 11, the tube 220, along at least a portion of its

length, may be disposed within the lumen 218. The distal tip of the tube 220 is positioned along the longitudinal axis of lumen 218 and secured in place by one or more centering fins or spacers 222.

5 The catheter 214 also may include a lumen 224 through which blood proximate the distal tip 226 of the catheter 214 may be drawn, e.g., to provide a blood sample for use in determining blood pO_2 or in the monitoring of others clinical parameters, to ascertain blood pressure at the distal end of the catheter, etc.

10 The distal tip 226 of catheter 214 includes an ultrasonic bubble detector 228 or similar assembly for detecting the presence of clinically significant bubbles in the oxygen-enriched fluid delivered to the patient body via lumen 218. Accordingly, the catheter 214 may also include one or more lumens 230 within which leads coupled to the bubble detector 228 are disposed.

15 Figures 12-14 illustrate alternate exemplary tip configurations of a catheter. Figure 12 shows a straight tip portion 232 including a bubble detector 236 disposed proximate the tip 234 of the catheter. Bubble detector leads 238 comprising one or more pairs of insulated wires or coaxial wires may be disposed as shown for example in Fig. 12A within the catheter side wall. Figure 13 illustrates a straight tip portion 240 including a dual transducer bubble detector 242,
20 bubble detector leads 244, and a monorail guide lumen 246 through which a guidewire (not shown) may be thread to assist in the placement of the catheter within a patient body. One transducer of a dual transducer bubble detector typically emits an acoustic pulse which is received by the other transducer, and the presence or absence of bubbles is determined by

measuring the attenuation of the received signal. Figures 14 and 14A illustrate alternate configurations of a catheter tip including a monorail guide lumen 248. The catheter tip as shown in the drawings may include a relatively uniform wall thickness and be of generally circular cross section (Fig. 14), or it may have a varying wall thickness and assume a more tear-drop shape (Fig. 14A).

As shown in Fig. 12, a catheter tip also may include a radiopaque band 250 to aid the physician or caregiver in placing the device. Typically, the band 250 comprises one or more metals or metal alloys, e.g., platinum, gold, tungsten, and iridium, and platinum-iridium and other high density materials that are visible under fluoroscopy.

A further exemplary bubble detector transducer 252 is shown in FIGS. 15 and 15A. The transducer 252, which may be bonded or otherwise fixedly attached to or within the distal portion of the catheter, may include a single transducer operable in a pulse echo mode, i.e., it can send out an acoustic pulse and sense its reflection. The transducer 252 includes an inner sleeve 254, a layer of wrapped piezo-electric film 256, a metal band 258, and an outer jacket 260. The inner sleeve 254 comprises a polyimide sleeve. The wrapped film 256 comprises a metallized polyvinylidene fluoride (PVDF) film including a conductive upper layer 262, a conductive lower layer 264, and an insulative inner layer 263 separating the upper and lower layers. As shown in the drawings, the metallized film is folded and then wrapped at least once (typically about two to five times) about the inner sleeve 254. This folding permits the use of thinner film that exhibits higher capacitance and lower impedance than a more conventional transducer so that the wire leads 266, which are long, thin wires, may be driven better. Wire leads 266 are connected to the

outermost surfaces of the layers 262, 264 with a conductive epoxy 268. The band 258 may comprise a foil of aluminum or a band of a metal which reflects the outward acoustic pulse. The band 258 comprises a radiopaque material so that the band may also act as a marker to promote placement of the device. The outer jacket 260 may be made of pebax or another suitable material which provides support to the structure. It should further be understood that the bubble detector illustrated in Figs. 15 and 15A is advantageously a compact device, e.g., air spaces between the layers of the bubble detector are minimized or eliminated. For example, any air voids may be filled with an epoxy or other suitable filler material.

The electronic circuitry 271 associated with the bubble detector transducer 252 causes the transducer 252 to emit ultrasonic pulses typically in the range of 20-30 MHz. In the pulse echo mode, these ultrasonic pulses are transmitted in a pulse train having a frequency of about 20-50 kHz. Thus, approximately ten reflections may be sampled from a single bubble as it passes by the transducer 252, which is about 1 to 1.5 millimeters in length. After the pulses of ultrasonic energy are delivered during a positive portion of this duty cycle, the circuitry 271 waits approximately 0.5 microseconds to allow for a "ring down" period. Then, the reflected signals may be measured, typically for at least three bounces, before the next ultrasonic signals are transmitted.

The present invention has been described in terms of exemplary embodiments. In accordance with the present invention, the operating parameters for the system may be varied, typically with a physician or caregiver specifying and selecting them for the desired clinical indication. Further, it is contemplated that other embodiments, which may be readily devised by

persons of ordinary skill in the art based on the teachings set forth herein, may be within the scope of the invention which is defined by the appended claims. The present invention may be modified and practiced in different but equivalent manners that will be apparent to those skilled in the art having the benefit of the teachings set forth herein.

5

No limitations are intended to the details or construction or design shown herein, other than as described in the claims appended hereto. Thus, it should be clear that the specific embodiments disclosed above may be altered and modified, and that all such variations and modifications are within the spirit and scope of the present invention as set forth in the claims appended hereto.

10

CLAIMS**WHAT IS CLAIMED IS:**

1. An apparatus for the preparation of a gas-enriched fluid, the apparatus comprising:

5 means for supplying a first fluid comprising a gas-supersaturated liquid;

means for supplying a second fluid; and

means for combining the first and second fluids to form the gas-enriched fluid.

10 2. The apparatus of claim 1 wherein the combining means comprises a catheter including a central lumen in fluid communication with the means for supplying the first and second fluids.

15 3. The apparatus of claim 1 wherein the first fluid comprises an oxygen-supersaturated fluid.

4. An apparatus for the preparation of a gas-enriched fluid, the apparatus comprising:

an assembly including first and second lumens;

the first lumen in fluid communication with a first fluid supply; and

the second lumen in fluid communication with a second fluid supply of a gas-supersaturated fluid and with the first lumen.

5. The apparatus of claim 4 wherein the second fluid comprises an oxygen-supersaturated fluid.

6. The apparatus of claim 4 wherein a portion of the assembly is removably insertable within a patient's body.

7. The apparatus of claim 4 wherein the gas-enriched fluid is a physiologic solution.

8. The apparatus of claim 4 wherein the gas-enriched fluid comprises blood.

9. The apparatus of claim 4 wherein the gas-enriched fluid comprises oxygen-enriched blood.

5 10. The apparatus of claim 4 wherein the gas-enriched fluid comprises an oxygen-supersaturated fluid and blood.

10 11. The apparatus of claim 4 wherein the gas-enriched fluid comprises a blood substitute.

12. The apparatus of claim 4 wherein the gas-enriched fluid comprises blood plasma.

15 13. An apparatus for the delivery of a gas-enriched fluid to a site, the apparatus comprising:

20 a first assembly comprising an elongated generally tubular member including proximal and distal ends and a lumen comprising a continuous fluid flow path between the proximal and distal ends, the distal end disposed proximate to the site to which the gas-enriched fluid is to be delivered; and

a second assembly comprising at least one elongated generally tubular member including first and second ends and at least one lumen comprising a continuous fluid flow path between the first and second ends, the second end disposed within the lumen of the first assembly, the first end of the second assembly adapted to be coupled to a supply of a first fluid, the first fluid comprising a gas-supersaturated fluid, and the proximal end of the first assembly adapted to be coupled to a supply of a second fluid.

5

14. The apparatus of claim 13 wherein the second assembly comprises a plurality of elongated generally tubular members, each member including first and second ends and at least one lumen comprising a continuous flow path between the first and second ends, the second ends disposed within the lumen of the first assembly.

5

15. The apparatus of claim 13 wherein the second assembly lumen has an internal diameter of between about 20 microns and 1000 microns.

10

16. The apparatus of claim 13 wherein the second assembly lumen has an internal diameter of between about 100 microns to 125 microns.

15

17. The apparatus of claim 13 wherein at least a portion of the first assembly including the distal end is removably insertable within a patient's body.

20

18. The apparatus of claim 17 wherein the removably insertable portion is insertable through a body access port.

19. The apparatus of claim 18 wherein the body access port comprises a guiding catheter.

5 20. The apparatus of claim 18 wherein the body access port comprises a sheath.

21. An apparatus for increasing fluid oxygen levels, the apparatus comprising:

10 means for providing a supply of a first fluid;

means for providing a supply of a second fluid comprising a gas-supersaturated liquid;

and

15 an assembly including first and second lumens, the first lumen in fluid communication with the first fluid supply means, the second lumen in fluid communication with the second fluid supply means and with the first lumen.

20 22. The apparatus of claim 21 wherein the first fluid comprises blood.

23. The apparatus of claim 22 wherein the oxygen level increased is the level of dissolved oxygen in the blood.

5 24. The apparatus of claim 21 wherein the oxygen level increased is the oxygen saturation level of an oxygen carrier.

25. The apparatus of claim 24 wherein the oxygen carrier is hemoglobin.

10 26. The apparatus of claim 24 wherein the oxygen carrier is a blood substitute.

15 27. The apparatus of claim 22 wherein the oxygen level increased is the concentration of oxygen in the blood.

20 28. The apparatus of claim 22 wherein the oxygen level increased is the blood partial pressure of oxygen.

29. The apparatus of claim 21 wherein the means for providing a supply of a first fluid comprise a means for withdrawing blood from a patient body.

5 30. The apparatus of claim 21 wherein the means for providing a supply of a first fluid includes a blood pump.

31. A catheter comprising:

10 a first elongated generally tubular member including proximal and distal ends, the first member including a lumen comprising a continuous fluid pathway between the proximal and distal ends; and

15 a second elongated generally tubular member including proximal and distal ends, the second member coupled to the first member, the second member including a lumen comprising a continuous fluid pathway between the proximal end of the second member and the fluid pathway between the proximal and distal ends of the first member.

20 32. The catheter of claim 31 wherein a portion of the first member proximate to its distal end is removably insertable into a patient's body.

33. The catheter of claim 32 wherein the insertable portion of the first member includes at least one port in fluid communication with the fluid pathway between the proximal and distal ends of the first member.

5

34. The catheter of claim 32 wherein the proximal end of the first member is adapted to provide a continuous fluid pathway between a supply of blood and the fluid pathway between the proximal and distal ends of the first member.

10

35. The catheter of claim 32 wherein the proximal end of the second member is adapted to provide a continuous fluid pathway between a supply of gas-supersaturated fluid and the fluid pathway between the proximal end of the second member and the fluid pathway between the proximal and distal ends of the first member.

15

36. A catheter comprising:

a first elongated generally tubular member including proximal and distal ends, the first member including a lumen comprising a continuous fluid pathway between the proximal and distal ends; and

20

a plurality of side members, each side member comprising an elongated generally tubular

member including proximal and distal ends, the side members coupled to the first member, each side member including a lumen comprising a continuous fluid pathway between the proximal ends of the side members and the fluid pathway between the proximal and distal ends of the first member.

5

37. A device for combining a first fluid with a second gas-supersaturated fluid, the device comprising:

10 a housing having therein a first fluid passageway having a first end and a second end and a second fluid passageway having a first end and a second end, the second end of the second fluid passageway intersecting the first fluid passageway at a junction between the first and second ends of the first fluid passageway, the first end of the first fluid passageway being adapted to receive a first line for supplying the
15 second gas-supersaturated fluid, and the first end of the second fluid passageway being adapted to receive a supply of the first fluid, the first line having an outlet positioned in a substantially laminar flow region of the first fluid passageway.

20 38. The device of claim 37, wherein the second end of the first fluid passageway is adapted to receive a proximal end of a first catheter, the first catheter having a distal end adapted to be positioned within a patient's body for delivering a combination of the first fluid and the second gas-supersaturated fluid to a site within the patient's body.

39. The device of claim 38, wherein the outlet of the first line is positioned downstream from the proximal end of the first catheter.

5 40. The device of claim 38, wherein the outlet of the first line is positioned upstream from the proximal end of the first catheter.

10 41. The device of claim 37, wherein the outlet of the first line is positioned between the junction and the second end of the first fluid passageway.

15 42. The device of claim 37, wherein the outlet of the first line is positioned between the first end of the first fluid passageway and the junction.

 43. The device of claim 37, wherein the outlet of the first line is positioned at the junction.

20 44. The device of claim 37, wherein the first line comprises a plurality of wings for supporting the first line within the first fluid passageway.

45. The device of claim 37, wherein the first fluid passageway is angled relative to the second fluid passageway at an acute angle.

5 46. The device of claim 37, wherein the first fluid comprises blood and wherein the second fluid comprises oxygen-supersaturated fluid.

10 47. The device of claim 37, further comprising a pump coupled to supply the first fluid to the second fluid passageway.

15 48. The device of claim 47, comprising a second catheter having a proximal end and a distal end, the proximal end being coupled to an inlet of the pump, and the distal end being adapted to be positioned within a patient's body for delivering the first fluid from the patient's body to the pump, and comprising a tube coupled between an outlet of the pump and the first end of the second fluid passageway for delivering the first fluid to the second fluid passageway.

20 49. The device of claim 38, further comprising a microbubble detector disposed proximate the distal end of the first catheter.

50. A method for forming a gas-enriched fluid comprising:

providing a supply of a first fluid;

5 combining the supply of first fluid with a gas-supersaturated fluid to form the gas-enriched fluid.

51. The method of claim 50 wherein the first fluid comprises blood.

10

52. The method of claim 50 wherein the gas-supersaturated fluid comprises an oxygen-supersaturated fluid.

15

53. The method of claim 50 wherein the first fluid comprises a blood substitute.

54. The method of claim 50 wherein the gas-enriched fluid comprises an oxygen-enriched physiologic liquid.

20

55. A method for the delivery of a gas-enriched fluid comprising:

providing a supply of a first fluid;

5 providing a supply of a gas-supersaturated fluid;

forming the gas-enriched fluid by combining within a catheter the first fluid and the gas-supersaturated fluid; and

10 transferring the gas-enriched fluid from the catheter to a patient.

56. The method of claim 55 wherein the first fluid comprises blood.

15

57. The method of claim 55 wherein the gas-supersaturated fluid comprises an oxygen-supersaturated fluid.

20 58. The method of claim 55 wherein the transfer of the gas-enriched fluid is through the catheter to predetermined site within a human body.

59. The method of claim 58 wherein the site is proximate the heart.

60. The method of claim 58 wherein the site is proximate the brain.

61. The method of claim 58 wherein the site is within a circulatory vessel.

62. A method for increasing a blood oxygen level comprising combining blood with an oxygen-supersaturated fluid.

63. The method of claim 62 wherein the blood oxygen level increased is blood partial pressure of oxygen.

64. The method of claim 62 wherein the blood oxygen level increased is hemoglobin saturation.

65. The method of claim 63 wherein the blood partial pressure is increased to over about 90-110 mm Hg.

66. The method of claim 63 wherein the blood partial pressure is increased to over about 500 mm Hg.

5 67. The method of claim 63 wherein the blood partial pressure is increased to about 760 mm Hg.

10 68. The method of claim 63 wherein the blood partial pressure is increased to over 760 mm Hg.

69. A method of forming a gas-enriched fluid, the method comprising the acts of:

- 15 (a) flowing a first fluid through a first fluid passageway;
- (b) flowing a second gas-supersaturated fluid through a second fluid passageway; and
- 20 (c) combining the first fluid with the second gas-supersaturated fluid at an intersection between the first fluid passageway and the second fluid passageway to form the gas-enriched fluid.

70. The method of claim 69, wherein act (a) comprises the act of:

coupling the first fluid passageway to a supply of the first fluid.

5

71. The method of claim 69, wherein the first fluid comprises blood.

72. The method of claim 70, wherein act (a) comprises the acts of:

10

placing a distal end of a catheter within a patient's body to withdraw the blood;

coupling a proximal end of the catheter to an inlet of a pump;

15

coupling a first end of a tube to an outlet of the pump; and

coupling a second end of the tube to the first fluid passageway.

20

73. The method of claim 69, wherein act (b) comprises the act of:

coupling the second fluid passageway to a supply of gas-supersaturated fluid.

74. The method of claim 69, wherein act (c) comprises the act of:

combining the first fluid and the second gas-supersaturated fluid in a region of substantially laminar flow.

5

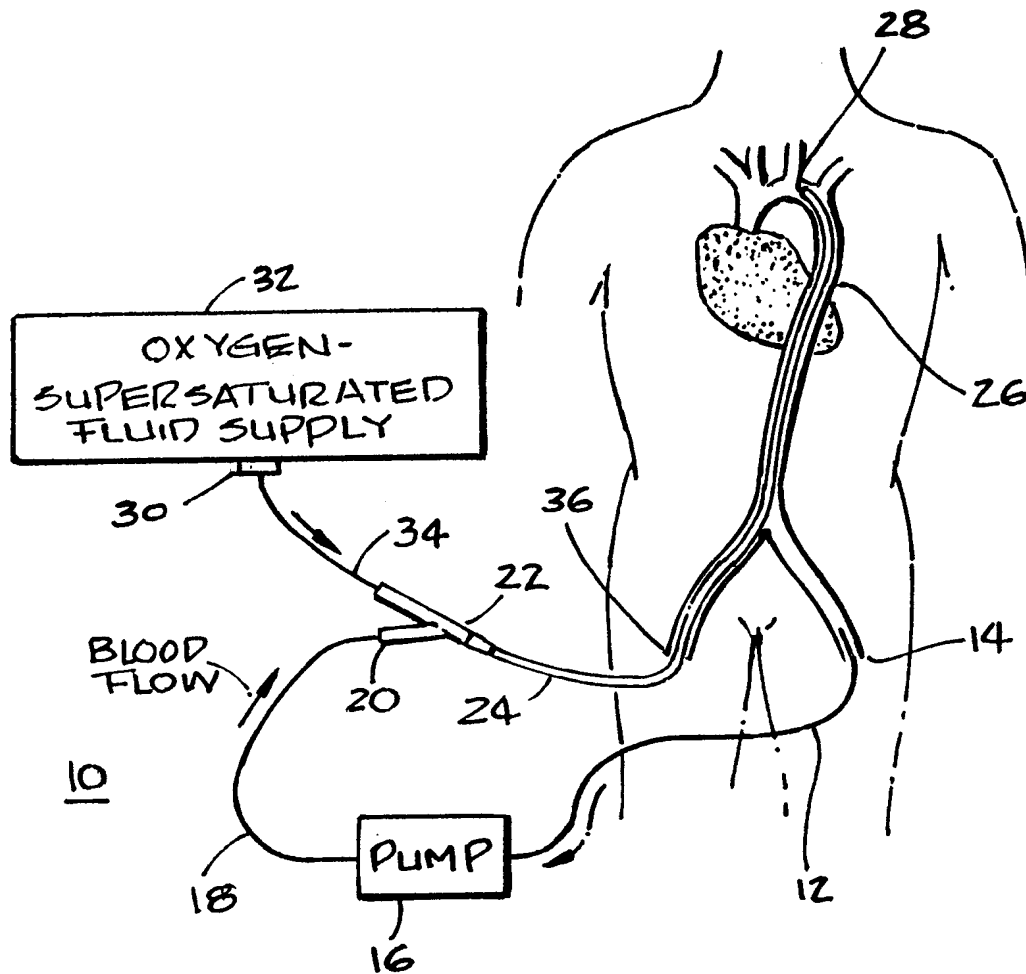
75. The method of claim 69, wherein act (c) comprises the act of:

combining the first fluid and the second gas-supersaturated fluid within a proximal

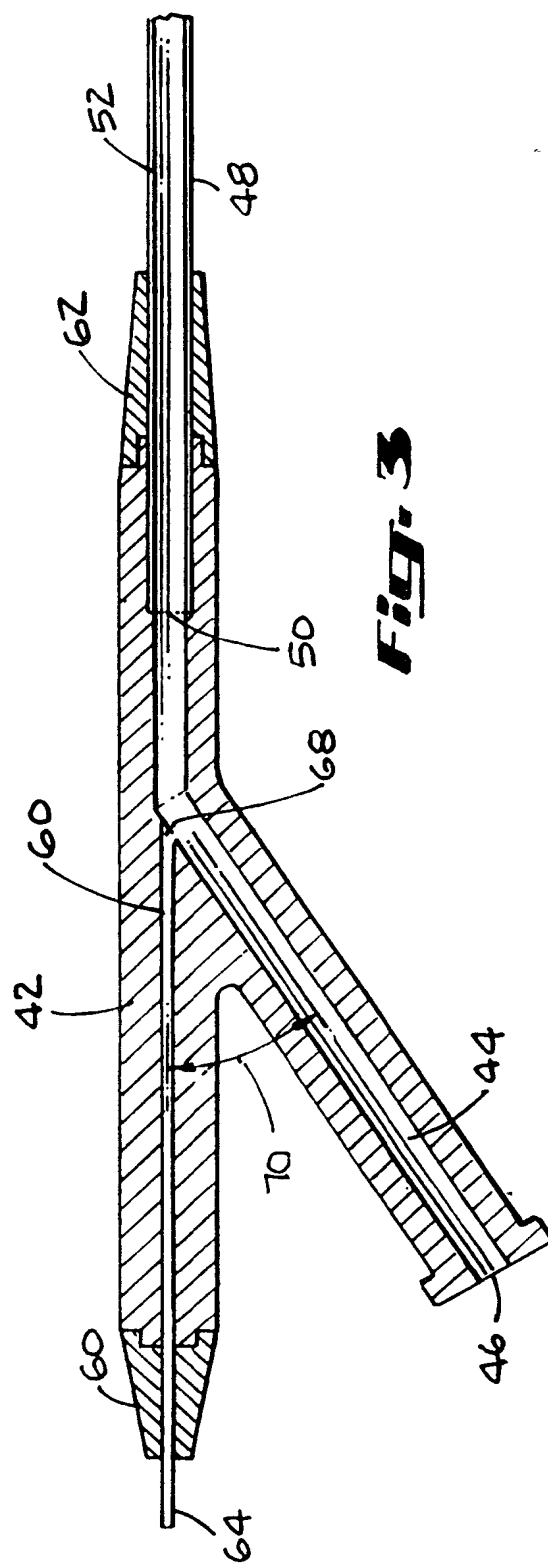
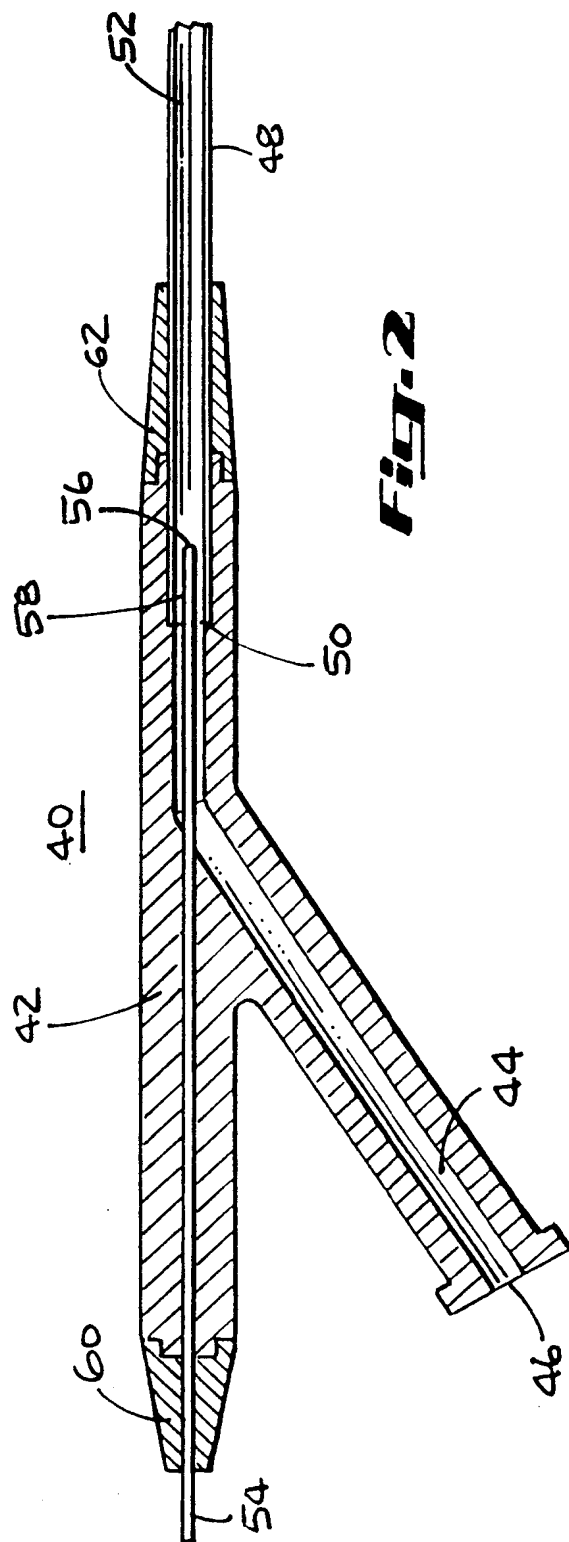
10

portion of a catheter device, wherein the catheter device comprises a distal portion adapted to be positioned within a patient's body for delivering the gas-enriched fluid to a site within the patient's body.

1/11

***Fig. 1***

2/11



3/11

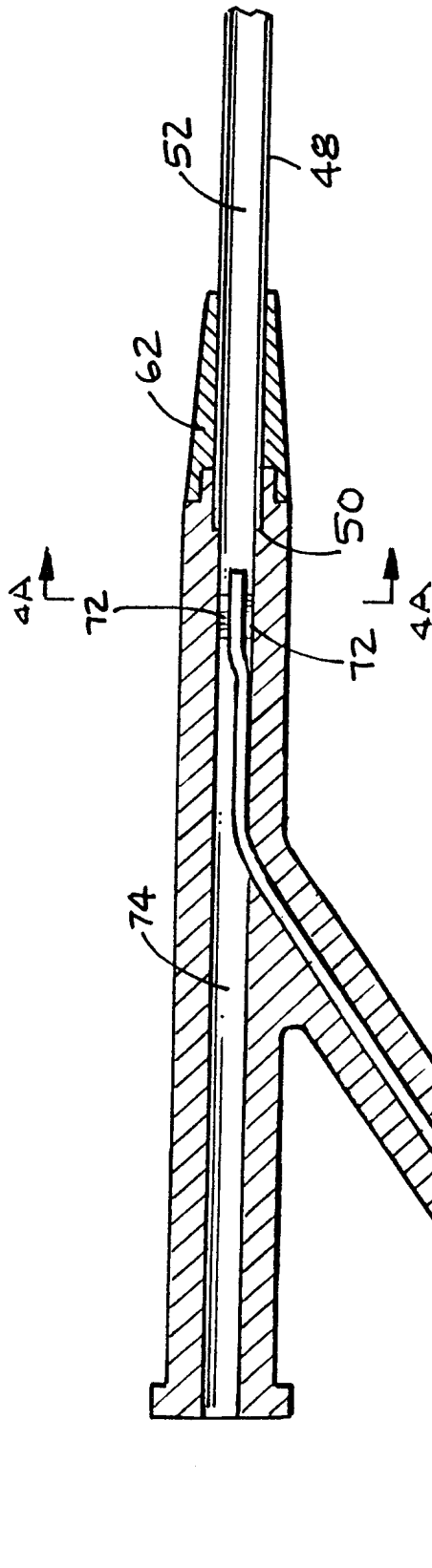


Fig. 1

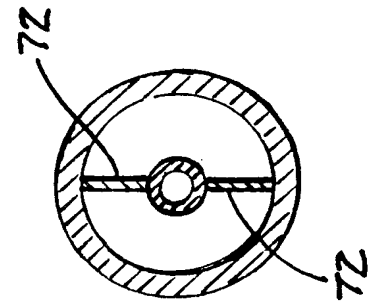


Fig. 1A

4/11

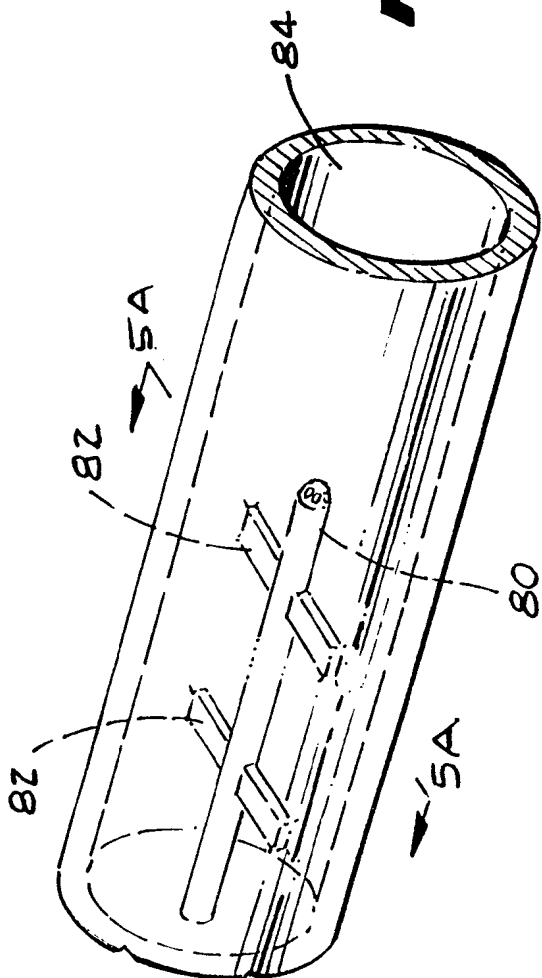


Fig. 5

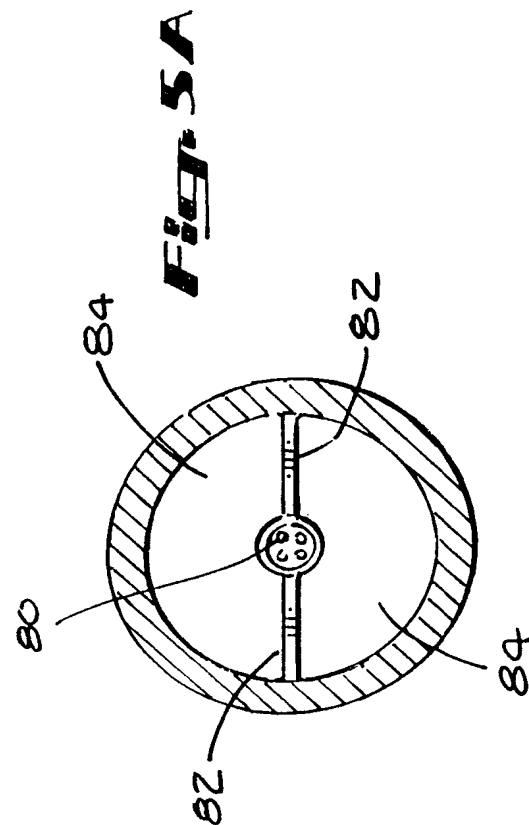


Fig. 5A

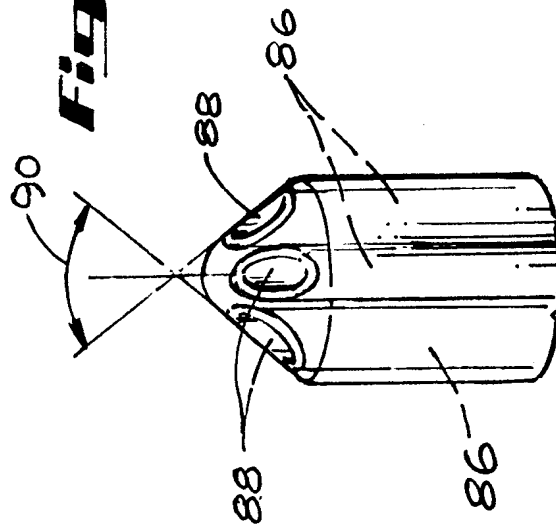


Fig. 5B

5/11

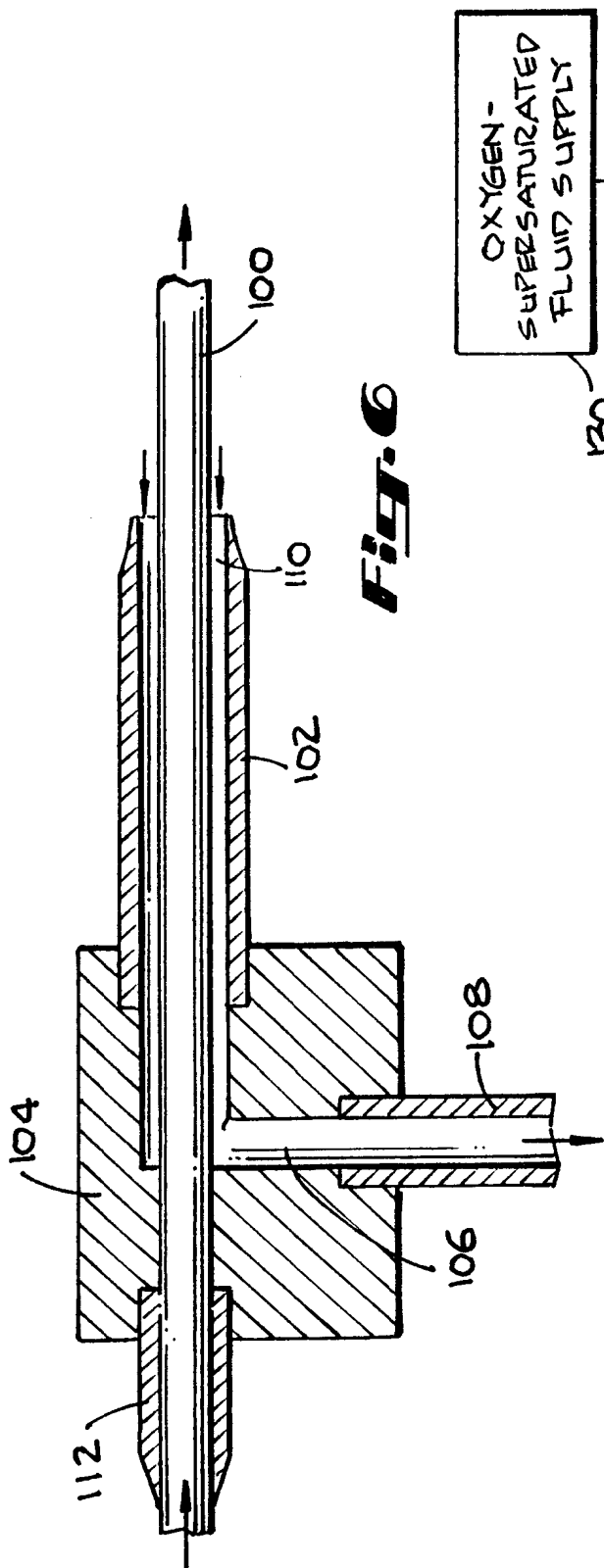


Fig. 6

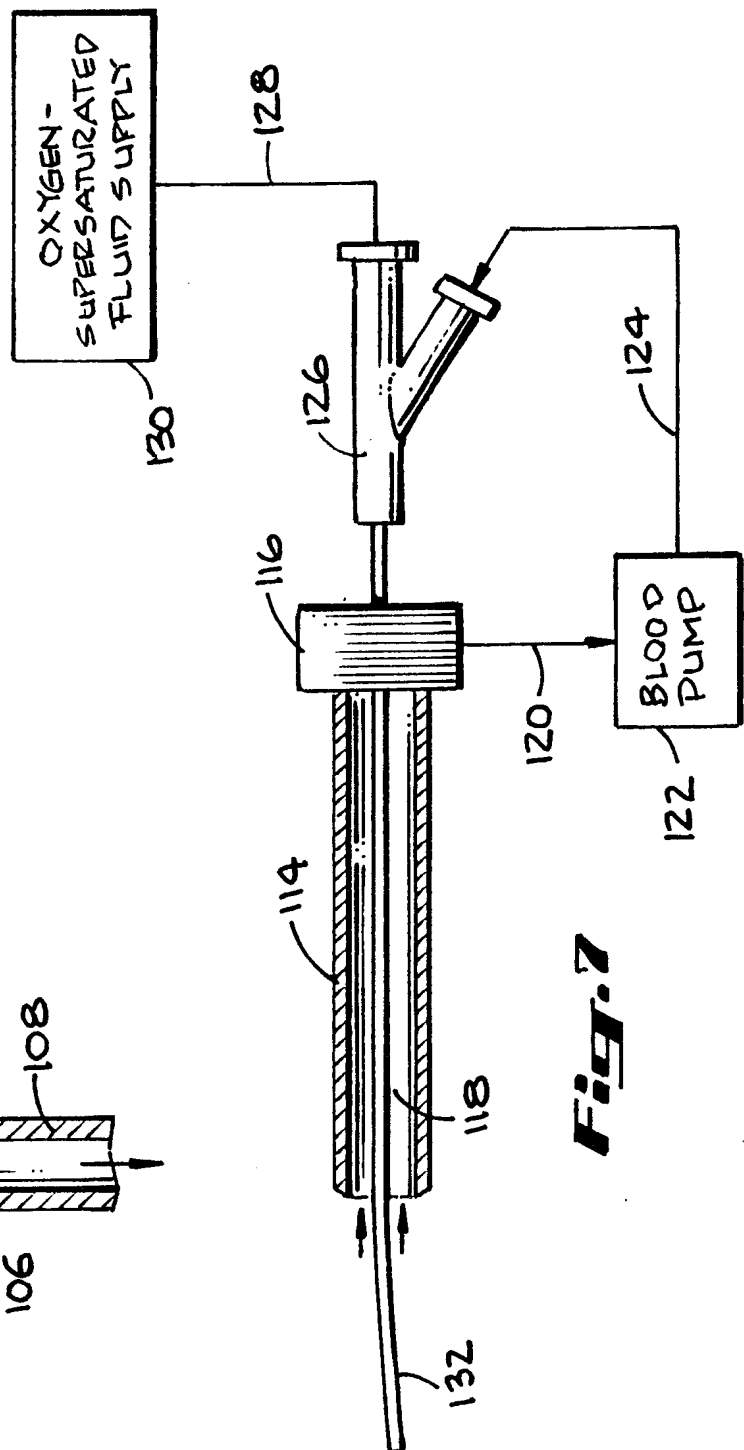


Fig. 7

6/11

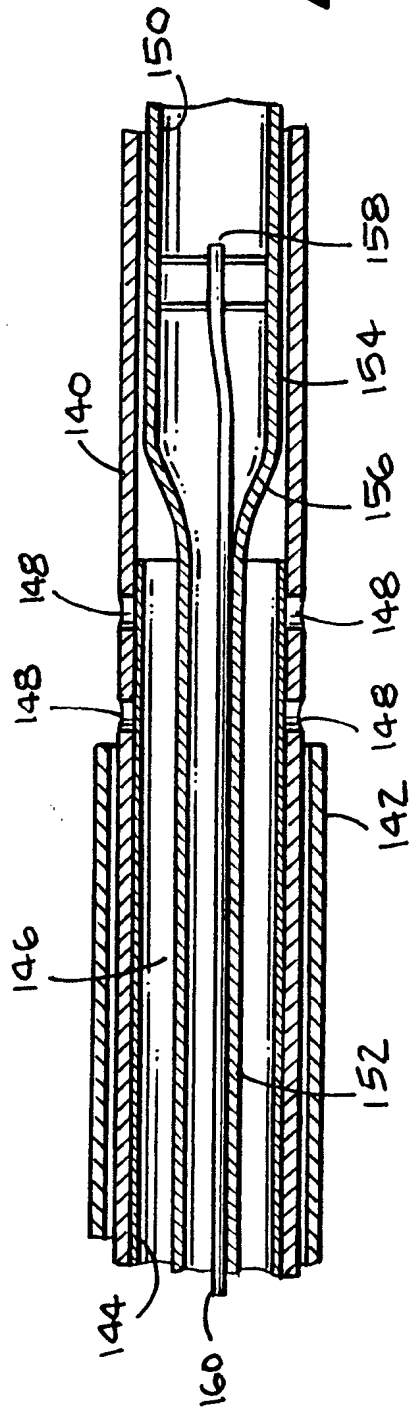


Fig. 8

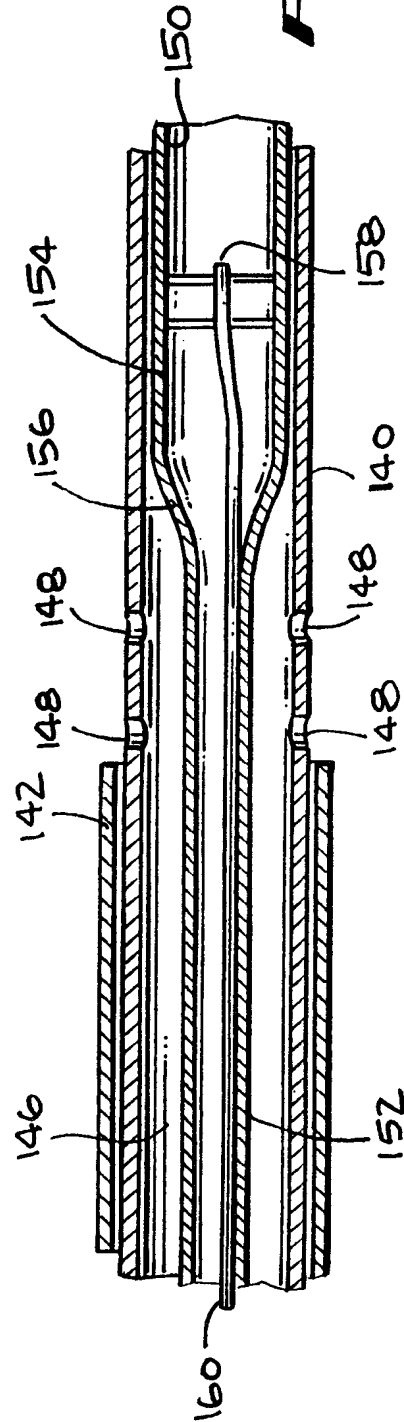


Fig. 8A

7/11

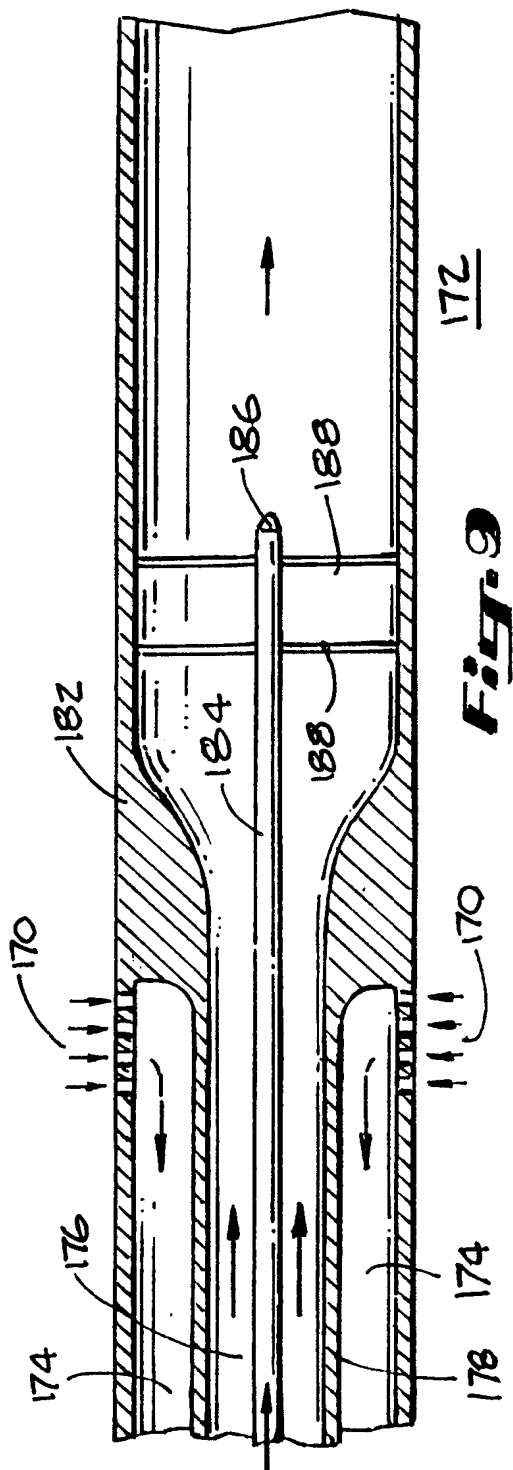


Fig. 9

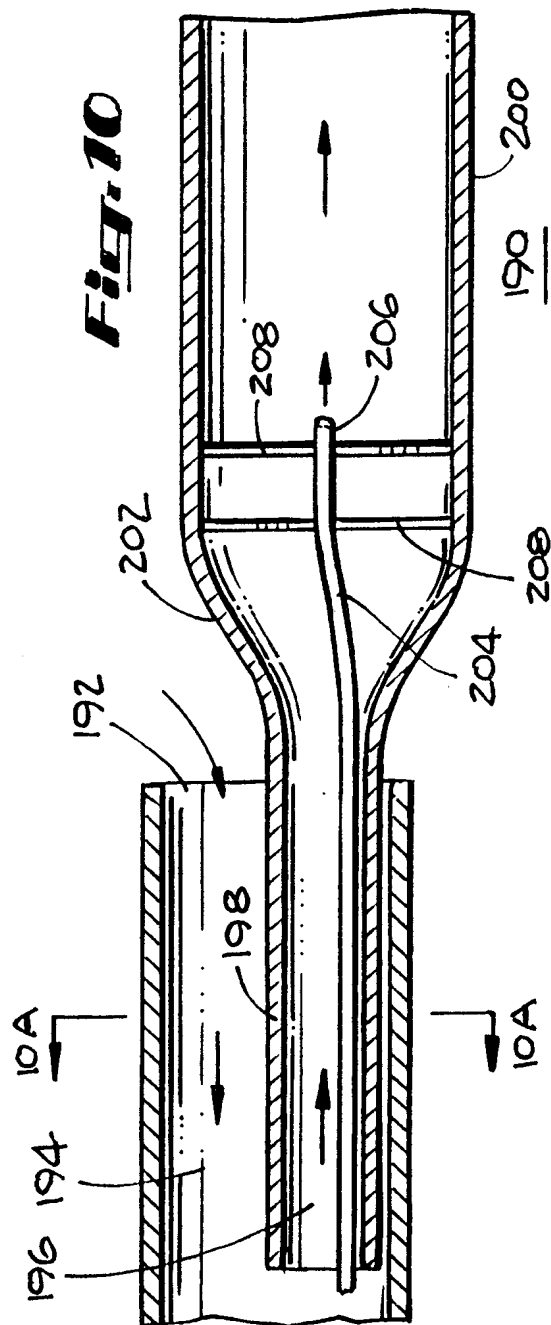


Fig. 10

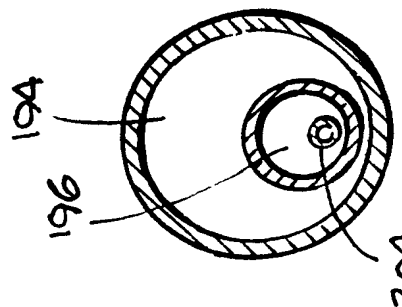


Fig. 10A

8/11

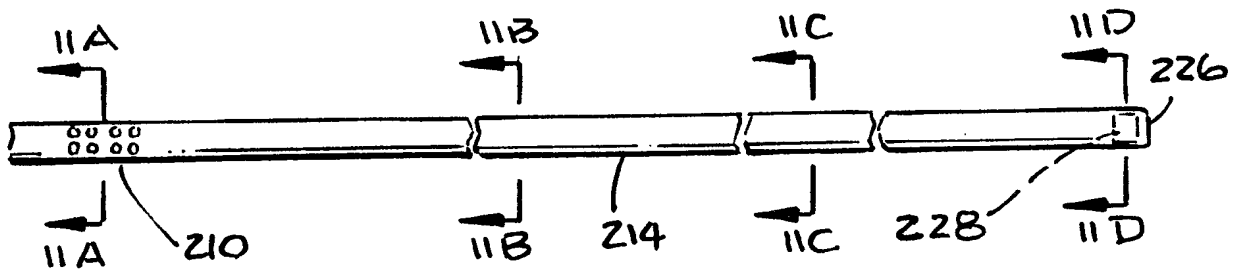


Fig. 11

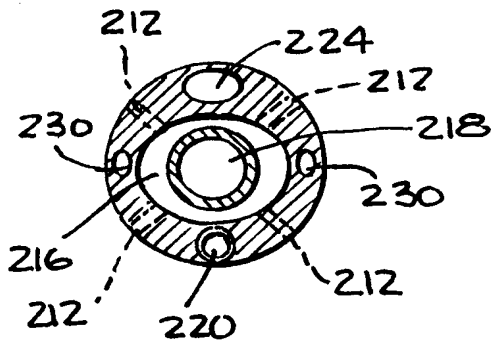


Fig. 11A

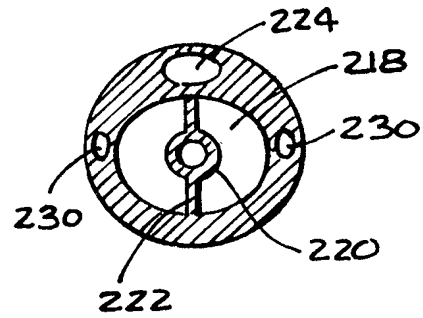


Fig. 11B

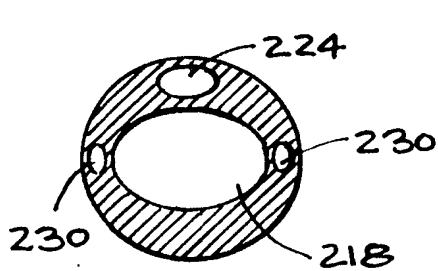


Fig. 11C

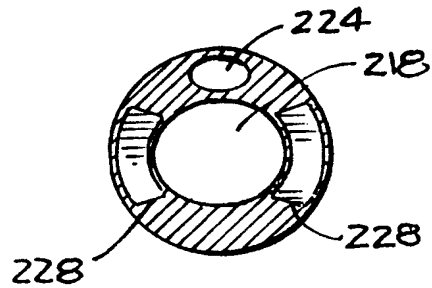


Fig. 11D

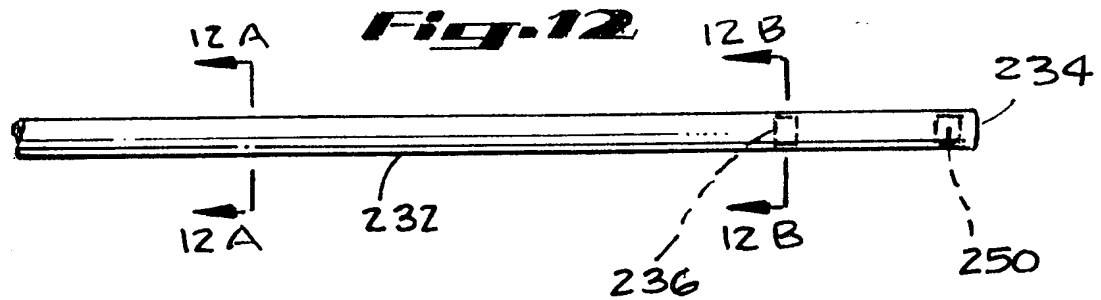


Fig. 12A

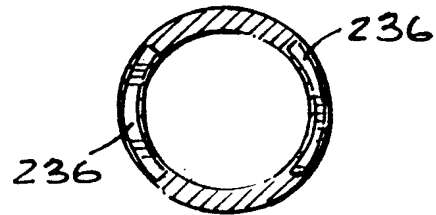
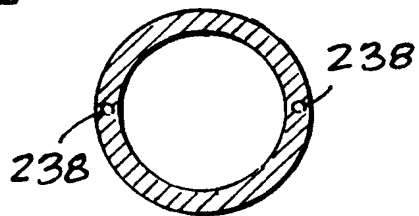


Fig. 12B

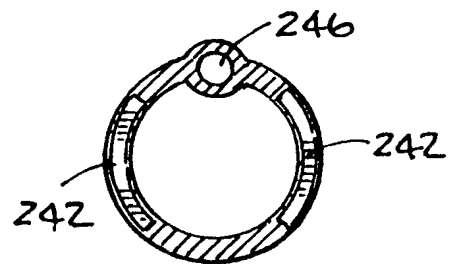
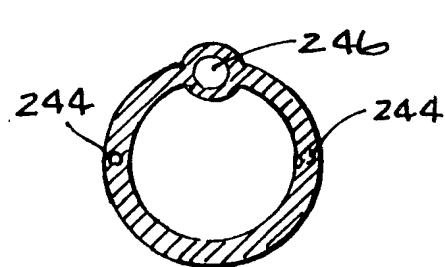
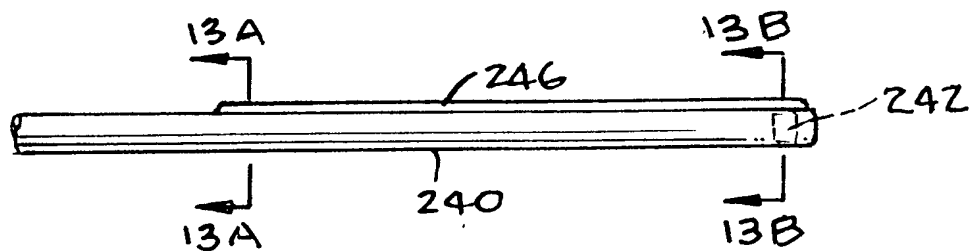


Fig. 13B

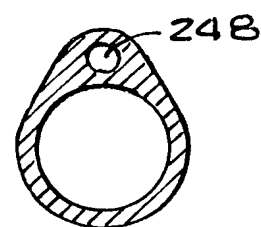
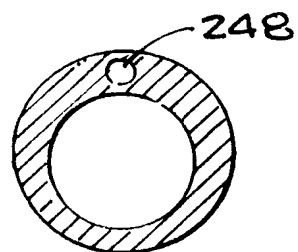
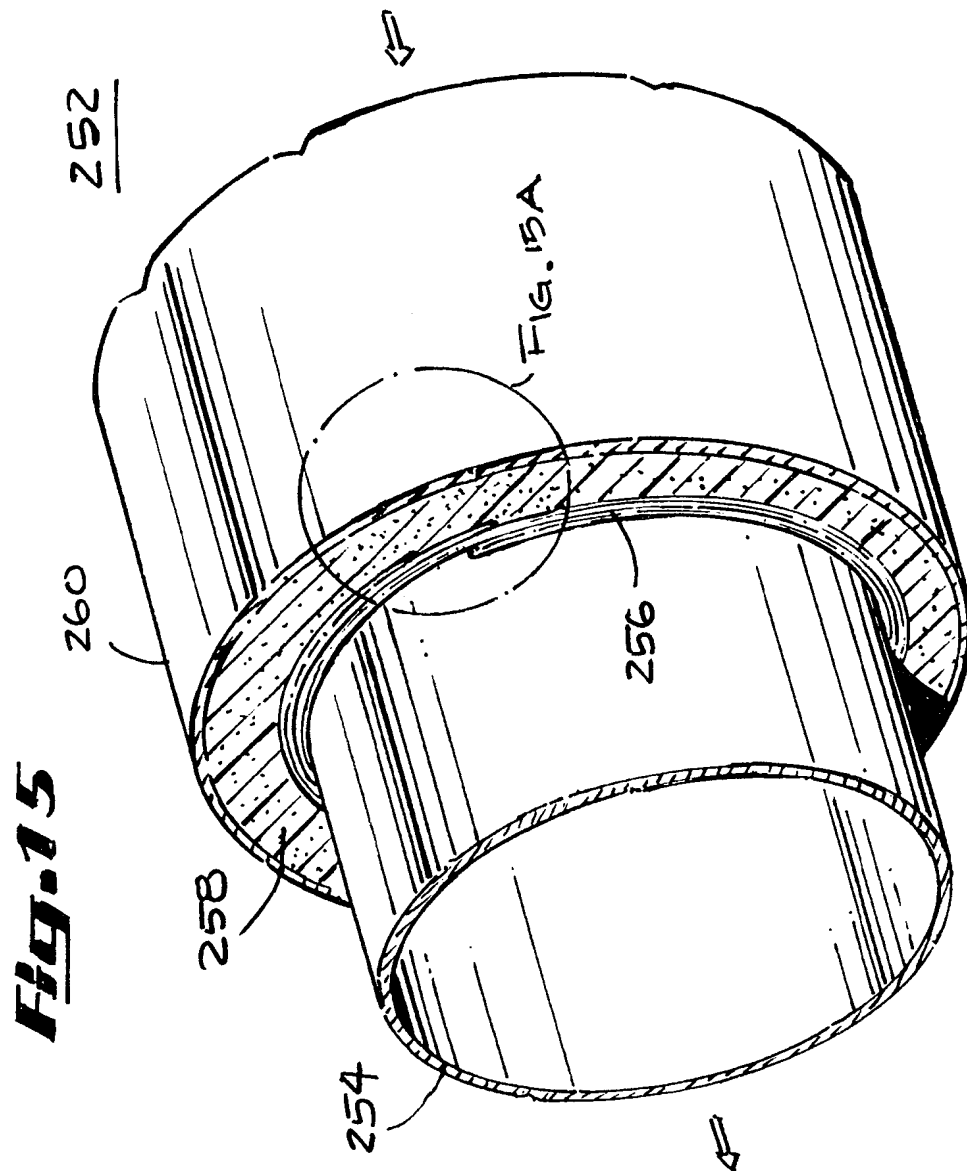
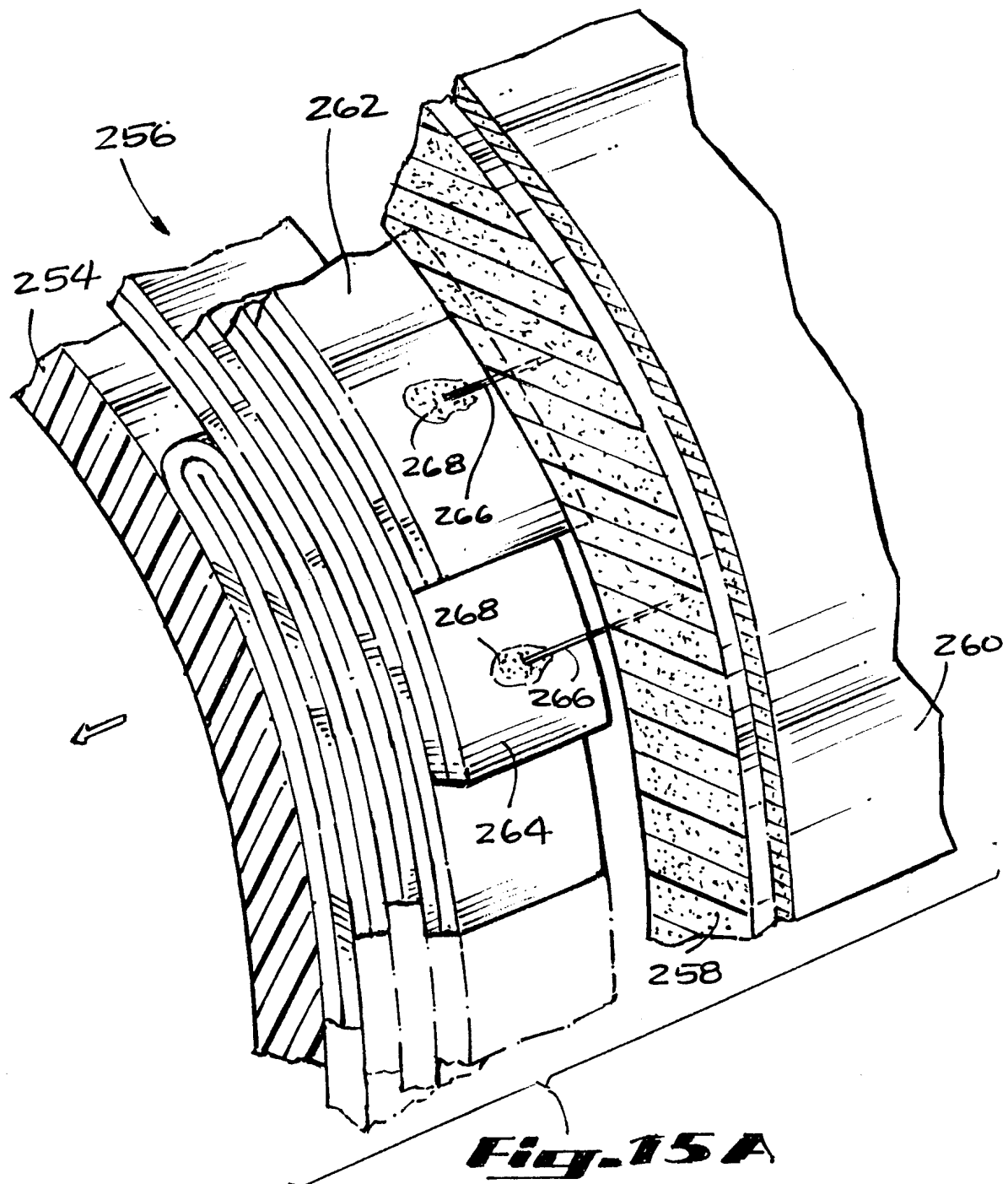


Fig. 14A

10/11





SUBSTITUTE SHEET (RULE 26)

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/16743

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61M1/32 A61M25/00 B01F3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61M B01F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|--|
| E | <p>WO 99 08733 A (THEROX, INC) 25 February 1999 (1999-02-25)</p> <p>the whole document</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p> | <p>1-10, 13, 14, 17-24, 27, 29, 30, 50-52, 69-71, 73, 74</p> |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

28 October 1999

Date of mailing of the international search report

04/11/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Schönleben, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/16743

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|--|
| X | US 4 664 680 A (WEBER) 12 May 1987 (1987-05-12) column 2, line 65 -column 3, line 45 column 7, line 1 -column 8, line 47 column 9, line 17 - line 46 figures 2,3 | 1,3-5, 13,21, 50,52, 69,70,73 |
| A | ---- | 37 |
| X | WO 95 13843 A (WAYNE STATE UNIVERSITY) 26 May 1995 (1995-05-26) page 4, line 6 -page 5, line 19 page 8, line 27 -page 10, line 3 page 14, line 29 -page 15, line 26 claims 12-18 | 1-3, 50-54 |
| A | & US 5 407 426 A cited in the application ---- | 14-16 |
| X | WO 96 17565 A (WAYNE STATE UNIVERSITY) 13 June 1996 (1996-06-13) page 9, line 16 - line 25 page 10, line 1 - line 12 page 18, line 1 - line 9 figure 1A | 31-33, 35,36 |
| A | & US 5 797 874 A cited in the application ---- | 15,16 |
| X | US 5 211 627 A (WILLIAM) 18 May 1993 (1993-05-18) column 2, line 40 -column 3, line 3 figures 1-4 ---- | 31-33 |
| X | US 4 802 650 A (STRICKER) 7 February 1989 (1989-02-07) column 3, line 5 - line 36 column 4, line 34 -column 5, line 43 figures 1,3,4 ----- | 37,38 |

INTERNATIONAL SEARCH REPORT

I. International application No.

PCT/US 99/ 16743

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 55-61, 62-68, 72, 75
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT-Method for treatment of the human or animal body by therapy.
Rule 39.1(iv) PCT-Method for treatment of the human or animal body by surgery.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/16743

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| WO 9908733 | A | 25-02-1999 | AU 9103998 A | 08-03-1999 |
| US 4664680 | A | 12-05-1987 | CA 1299778 A | 28-04-1992 |
| | | | DK 174487 A,B, | 08-10-1987 |
| | | | EP 0244954 A | 11-11-1987 |
| | | | IL 82063 A | 29-04-1990 |
| | | | JP 62277130 A | 02-12-1987 |
| WO 9513843 | A | 26-05-1995 | US 5407426 A | 18-04-1995 |
| | | | AU 1090595 A | 06-06-1995 |
| | | | CA 2176601 A | 26-05-1995 |
| | | | EP 0729369 A | 04-09-1996 |
| | | | JP 9509072 T | 16-09-1997 |
| | | | US 5569180 A | 29-10-1996 |
| | | | US 5599296 A | 04-02-1997 |
| | | | US 5735934 A | 07-04-1998 |
| | | | US 5797874 A | 25-08-1998 |
| | | | US 5693017 A | 02-12-1997 |
| | | | US 5730935 A | 24-03-1998 |
| WO 9617565 | A | 13-06-1996 | US 5599296 A | 04-02-1997 |
| | | | AU 4418196 A | 26-06-1996 |
| | | | CA 2207410 A | 13-06-1996 |
| | | | EP 0906071 A | 07-04-1999 |
| | | | JP 10510186 T | 06-10-1998 |
| | | | US 5797874 A | 25-08-1998 |
| | | | US 5693017 A | 02-12-1997 |
| | | | US 5730935 A | 24-03-1998 |
| US 5211627 | A | 18-05-1993 | NONE | |
| US 4802650 | A | 07-02-1989 | NONE | |